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The Journal of Allergy

VOL. 8 MAY, 1937 NO. 4

Original Articles

THE DRY POLLEN NASAL TEST*

ITS TECHNIC, INTERPRETATION, AND INDICATIONS

GEORGE I. BLUMSTEIN, M.D.
PHILADELPHIA, PA.

ALLERGIC patients often present histories of seasonal hay fever or asthma that cannot be corroborated by skin tests. Likewise, one often encounters positive skin reactions to pollen in the absence of a history of clinical sensitivity. Heretofore, it was the practice of most allergists to disregard negative skin tests, and treat seasonal cases with the pollen prevalent during the period of symptomatology. Although gratifying results were obtained with this method, there were also a number of failures. This would suggest the necessity of some objective procedure to evaluate the accuracy of histories or skin tests in cases where they are not in harmony. Such a test would consist in allowing the suspected allergen to contact the shock organ and note whether clinical symptoms followed. In suspected cases of pollinosis, cause and effect could be demonstrated in an objective way by allowing the patient to inhale the dry pollen. If the patient is clinically sensitive, a paroxysm of hay fever or asthma should thus be precipitated.

Blackley[1] was the first to utilize this method of testing in an attempt to identify the causes of hay fever. Dunbar[2] reported on its use in 1903. More recently Duke,[3] and Efron and Penfound,[4] have recommended its use in cases of pollinosis where the etiologic agents are doubtful because of numerous positive skin reactions. Rudolph and Cohen[5] reported on the value of the nasal test in cases of vasomotor rhinitis with negative skin tests.

The earliest trials in the present series made use of the sprayer as a means of instilling dry pollen into the nasal chambers. A few severe

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Read before the meeting of the Society for the Study of Asthma and Allied Conditions, May 2, 1936, Atlantic City.

reactions, including asthma, resulted because of the large amounts of pollen instilled, so that this method had to be abandoned. Attempts to control the amount of pollen applied by using a small wire loop failed because the pollen adhered to parts other than the loop. The technic that proved to be the safest and the most satisfactory was that of allowing the patient to inhale the dry pollen from the blunt end of a toothpick. The instillation was followed by a smarting sensation of the membrane that passed off in a few minutes, except in positive cases. By this method, sufficiently small quantities of pollen could be instilled into the nostrils to cause positive reactions in sensitive patients, and yet not cause symptoms in non-sensitive ones. A positive reaction depended on the production of symptoms similar to those from which the patient suffered; thus, if rhinorrhea was the predominating symptom, its reproduction would be recorded as a positive reaction. If the original instillation failed to produce symptoms, two additional applications were given at intervals of five minutes before the reaction was considered negative. All unpleasant reactions were alleviated by the instillation of nasal drops containing 1 per cent to 3 per cent ephedrine. Pine pollen, which does not contain an excitant of hay fever, was used as a control.

PROCEDURE

The subjects selected for this study were: first, patients with definite clinical sensitivity to pollens; second, patients with histories of seasonal asthma and hay fever, but negative skin tests; third, patients seen for the first time who showed marked skin sensitivity to pollens in the absence of definite clinical histories; and fourth, those patients who were known to have had hay fever, but in whom apparent remissions had occurred. The histories in all these cases were carefully reviewed and the periods of symptomatology noted. Skin tests were performed by the intracutaneous method, and all positive reactions to pollens were recorded. The dry pollen ophthalmic test was carried out in each case. This was done by applying to the everted lower lid conjunctiva a minute amount of dry pollen from the sharp end of a toothpick. The pollens utilized were timothy, plantain, and ragweed, all of which were used in each case. The other pollens employed were those that had produced positive skin reactions and those that by history were suspected of playing an etiologic rôle. After the removal of the pollen, annoying symptoms, resulting from positive reactions, were relieved by the instillation of 1:1,000 adrenalin. Nasal tests were done in all cases according to the method previously described by using the same pollens as in the ophthalmic tests. Pine pollen was used as a control in both the ophthalmic and nasal tests. To further ascertain the specificity of the nasal tests, it was decided to repeat them during the periods of active symptoms in patients who had previously given negative reactions to certain dry pollens.

RESULTS

One hundred patients were studied in this manner and a total of 422 nasal and ophthalmic tests were done. The results of the nasal tests in most cases were in agreement with the information obtained from the patients' histories. The tests were specific in all but 7 per cent of the cases. The nonspecific group reacted to any and every pollen instilled, including the control. These patients belong to the so-called hyperesthetic rhinitis group, and gave histories suggestive of perennial rhinitis without seasonal aggravation. In many of these cases, the conjunctiva also reacted to the instillation of dry pollen in a nonspecific manner. A positive nasal test in a patient suffering from hyperesthetic rhinitis must, therefore, be interpreted as a nonspecific reaction, and can be of no aid in identifying the offending agent. Positive nasal tests in all other cases were accompanied by positive ophthalmic reactions. The reverse, however, was not necessarily true, for in 175 positive ophthalmic tests only 117 or 67 per cent positive nasal tests were obtained. A positive ophthalmic test per se does not, therefore, indicate clinical sensitivity. Eight per cent of the patients studied showed nonspecific ophthalmic reactions.

Immediate negative nasal tests occurred in 6 patients who had apparent remissions, but delayed reactions followed in three of them. The skin and ophthalmic tests, however, remained positive in all instances. The following is a chart showing the number of tests performed, the type of pollen used in each case, and the correlation between the histories, skin, and ophthalmic and nasal tests, in the 100 cases studied.

TABLE I

POLLENS USED	NO. PATIENTS GIVING POSITIVE HISTORIES	NO. GIVING POSITIVE SKIN TESTS	OPHTHALMIC TEST		NASAL TEST		NO. WITH POSITIVE NASAL TESTS AND NEGATIVE HISTORY	NO. WITH NEGATIVE TESTS AND POSITIVE HISTORY	SPONTANEOUS REMISSION
			NO. PERFORMED	NO. POSITIVE	NO. PERFORMED	NO. POSITIVE			
Timothy	36	65	100	42	100	27	1	9	1
Plantain	3	52	100	26	100	10	7	–	–
Ragweed	73	83	100	77	100	67	6	7	5
Ash	–	16	16	1	16	1	1	–	–
Beech	–	15	15	2	15	–	–	–	–
Birch	–	11	11	4	11	–	–	–	–
Elm	–	8	8	3	8	2	2	–	–
Hickory	–	9	9	3	9	–	–	–	–
Maple	–	25	25	13	25	3	3	–	–
Oak	–	6	6	1	6	1	1	–	–
Poplar	1	17	17	7	17	3	2	–	–
Sycamore	–	14	15	6	15	3	3	–	–
Totals	113	321	422	175	422	117	26	16	6

It will be seen that of the 100 patients studied, 36 gave positive histories, 65 positive skin tests, 42 positive ophthalmic tests, but only 27 positive nasal tests to timothy pollen. The nine patients giving negative nasal tests in the presence of positive histories for timothy pollen, also had negative skin and ophthalmic tests. One patient with positive skin and ophthalmic tests and a negative history, yielded a positive nasal test for timothy pollen, and subsequent observation proved him to be clinically sensitive. By further analysis of the table it will be seen that positive nasal tests were obtained in 7 cases to plantain pollen, in 6 to ragweed pollen, and in 12 to various tree pollens, in the absence of positive histories. The nasal test corroborated the histories and skin tests in 86 per cent of the cases. It should not, therefore, be included as a routine procedure in studying allergic patients. Of the 117 positive nasal tests, 26 or 22 per cent yielded information that could not be obtained from histories and skin tests alone. In the majority of cases, by careful follow-up, it was possible to obtain histories of hay fever corresponding to the pollinating period of the pollen that yielded a positive nasal test.

DISCUSSION

The nasal test is of most value in those patients who give positive histories and multiple (positive) skin tests to pollens that are prevalent at or about the same time. With this test one can establish, by an objective method, the etiologic importance of the pollens which give positive skin reactions. It is of particular value in distinguishing the rôles played by plantain and grass pollens in the causation of the spring type of hay fever, as the pollinating periods of these two practically coincide.

Heretofore, a diagnosis of tree pollen hay fever was based on the correlation between history, skin tests, and field observation. The nasal test furnishes an office procedure that will often simplify the diagnosis of this type of hay fever. The test can also give valuable negative information. I refer to cases of seasonal asthma with negative skin and ophthalmic tests, for whom the pollen prevalent at that time is usually considered the causative agent. In nine such cases I have instilled large quantities of pollen (as much as 10 mg. in some) without reproducing the clinical picture. The failure to demonstrate cause and effect would tend to negate the etiologic importance of that particular pollen. A few of these cases who had received good results with pollen therapy were permitted to go through a pollinating season without such treatment, and in none of them did the asthma recur.

To further determine the specificity of this test, a group of 29 patients with hay fever symptoms were tested by the nasal route during the pollinating season with various pollens that had previously given nega-

tive nasal tests. In many of these patients, the introduction of the pollen was followed by considerable smarting, but in none of them did a positive reaction occur.

The nasal test has proved to be a safe procedure, void of the dangers of initiating severe reactions in this series of 100 patients. It is preferable to the spray method of introducing dry pollen into the nares, for in the latter, neither the quantity of pollen introduced nor the force with which it is applied can easily be regulated.

The disadvantages of the dry pollen nasal test are: first, it inconveniences the patient by artificially producing hay fever; second, only one such test can be done at any sitting, which is a time-consuming procedure; and finally, the sensitivity of the patient cannot be determined, nor the amount of pollen introduced regulated.

SUMMARY

1. A nasal test, consisting of the repeated instillation of small amounts of dry pollen, has been described.

2. The test gave a specific reaction in all but 7 per cent of the patients, in whom nonspecific reactions ensued as a result of hyperesthetic mucous membranes.

3. The specificity of the nasal test was further demonstrated by its failure to evoke a reaction during the period of active symptomatology, when the membranes are usually in a vulnerable state and tend to react to the slightest irritation.

4. The test has its greatest value in distinguishing the etiologic importance of pollens which yield positive skin tests and pollinate simultaneously, such as occur during the tree and grass seasons. It offers the allergist, who is too occupied to practice field observation, a simplified office procedure which can, in a number of cases, yield information that may be instrumental in making an accurate etiologic diagnosis.

5. In those patients in whom remissions were believed to have occurred, immediate negative nasal tests resulted, indicating that this method is of value in determining when a patient has had a remission.

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DISCUSSION

DR. LOUIS TUFT, Philadelphia.—As pointed out by Dr. Blumstein, the dry pollen nasal test finds its chief usefulness as an adjunct in diagnosis and not as a routine procedure. It has been proved to be of particular value, both in clinic and private practice, as a clinical test in those instances in which it was difficult to correlate the clinical history with the skin test findings, or vice versa. This is especially true of tree pollen sensitivity. For the past three years we have been studying those hay fever patients who give a history of so-called "spring cold" to determine the incidence and importance of tree sensitivity, and also to see whether this so-called "cold" was in reality a manifestation of tree pollen hay fever. In this study, which was reported before the Philadelphia Allergy Society last fall, the nasal test was found to be of considerable value in helping to differentiate sensitivity to those tree pollens whose pollination periods overlap or coincide, and particularly in patients whose history was rather indefinite. This test was found to be more useful as a clinical test in these patients than the dry pollen ophthalmic test. We have also been conducting a similar study of plantain pollen sensitivity, which we hope to report on shortly. The active period of symptoms in patients sensitive to plantain pollen often coincides with that of the grasses. When positive skin reactions are obtained to both pollens, it is often difficult to determine, from skin test evidence alone, which of these two groups is the major factor, and which of the two should be used in treatment. We have found the nasal test useful in these instances in helping to determine the relative importance of the two groups; in fact as with the trees, it has been found more useful than the ophthalmic test.

The only serious disadvantage or drawback to the test is the possibility of inducing active symptoms. It is this feature which has kept most allergists from using it in the past. If, however, the test is used only in selected cases when additional help is needed and not as a routine procedure; also if one observes the precautions of instilling only small amounts of pollen, and of employing a solution of ephedrine or adrenalin after a positive reaction is obtained, the risk of untoward reaction can be reduced to a minimum, and the test established as a safe and useful procedure. This test has been employed in our clinic a great many times, in a large number of patients, without any marked serious untoward reactions resulting. I believe, therefore, that this test has distinct clinical value as an adjunct in diagnosis in selected cases of pollen allergy.

DR. FRANCIS M. RACKEMANN, Boston.—Some years ago one of the men in the clinic thought he had hay fever in the month of June. At that time we were studying eye reactions and this individual thought he would like to try the test. He did not bother to do skin tests first. Some dry timothy pollen was placed in his eye, and within fifteen minutes he contracted an intense edema of both the upper and lower lids. He tried to wash it out of his eye without much success. He was incapacitated all of that afternoon, and had more or less trouble the next day. The eye test is not without danger.

DR. FERNAND VISTREICH, New York City.—The intranasal pollen test has the very important feature of being a close imitation of nature's

way to produce hay fever or hay asthma. Therefore, I think it is the most adequate test we can use in the determination of the patient's clinical sensitiveness.

The dry pollen test has one drawback in the fact that the quantity of pollen used in this test cannot be regulated sufficiently to use it as a quantitative index for the intranasal sensitiveness. I think even in the most precisely performed test we do not know how much pollen is inhaled into the nose and how much remains there. Modification of the intranasal pollen test is the pollen test with pollen solutions where we know exactly the quantity that we can introduce into the nasal cavity and observe its effects. We can even go so far as to use serial dilutions intranasally. This will enable us to determine, in rough way, quantitatively the grade of intranasal sensitiveness.

As to the interpretation of these reactions, I do not know whether I missed the point or whether it was entirely omitted from the paper. An intranasal reaction cannot be judged by the outward manifestations alone which the patient produces. I think the rhinoscopic picture is very important to be considered, because not every patient reacts with an attack of sneezing but with local edema and secretion.

There is one question that I would like to raise, that is whether Dr. Blumstein applied this test at the end of a successfully performed desensitization treatment, and whether he compared the reactions observed before and after treatment.

Dr. George Flamm, Brooklyn.—I have used this test in quite a number of patients. The cases that Dr. Blumstein describes are those in which we obtain a clinical or a seasonal history of hay fever, but the skin tests are fairly negative. In the type of case in which the skin test is entirely negative, even with a strong extract, we obtain only a slight or a moderate reaction and we often wonder whether that is a specific hay fever case or not.

It was in this group of cases with negative skins that I did both the ophthalmic and the intranasal tests. In all of the cases we found that the intranasal test was helpful in deciding whether there was any pollen sensitivity. The ophthalmic test was positive along with the intranasal test. The ophthalmic test was not done with the dry pollen but with the extracts. In the intranasal tests we at first started with the DeVilbiss powder blower, using dilutions. We mixed the dry pollen with talc, U.S.P. We mixed from one to ten, one to five, and one to two, and then the straight pollen. In the beginning, we used the intranasal test with the one to ten dilution, and then increased to the straight pollen if necessary.

We found that the DeVilbiss, as Dr. Blumstein described it, gave a little different reaction. In some cases the reactions were a little too severe. We then resorted to an ordinary pipette, and with that we were able to introduce a fixed amount of pollen into the nose, which we found was the best method of using the dry intranasal test.

In general, where the skin tests were negative, both the ophthalmic and intranasal tests were negative. In deciding if an intranasal test should be called positive, one must not judge merely by the sneezing or subjective symptoms of the patient. It is necessary to observe the changes in the nasal mucous membrane.

DR. BLUMSTEIN.—The question was asked as to the results before and after treatment. No accurate notation has been made of these, but we are trying at the present time, and hope to report on it at a later date. It seems that some cases that have been successfully treated have a greater tolerance for pollen after treatment than they do before. We have made no accurate notations on a large series of cases.

Dr. Rackemann mentioned the eye reaction. It is important that you remove the pollen, otherwise you will get a markedly swollen eye.

We did no nasal or eye tests on non-sensitive patients.

ALUM-RAGWEED PRECIPITATE: PREPARATION AND CLINICAL INVESTIGATION*

Preliminary Report

Albert R. Zoss, M.D., Carl A. Koch, M.D., and R. S. Hirose, Ph.D.
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THE successful use of alum toxoid in diphtheria immunization has served as a stimulus to investigations of alum-modified pollen extracts. In 1926 A. T. Glenny and his coworkers[1] precipitated diphtheria toxin and toxoid with alum, and demonstrated that a suspension of such a precipitate had high antigenic properties. In 1931 Glenny[2] reported that the increased antigenic efficiency of alum toxoid was due to its slow absorption and elimination. Harrison[3] in 1934 and Caulfeild[4] in 1936, reported the use of alum-treated ragweed extract in anaphylactic experiments in guinea pigs, and indicated its superiority over aqueous ragweed extract as a sensitizing agent. These investigators did not isolate the precipitated ragweed fractions, but employed mixtures of precipitated and unprecipitated ragweed extract.

The object of this study was to isolate the precipitate produced by the addition of potassium alum to aqueous ragweed extract, and to investigate the clinical activity of such a precipitate. Attempts were made first to determine whether this relatively insoluble precipitate was effective as a pollen antigen. Second, efforts were made to determine whether the precipitate would be retained in the body for longer periods of time than aqueous type extracts, and whether it would liberate its active pollen components more slowly, thereby possibly prolonging the period of antigenic stimulation and avoiding the occurrence of immediate toxic reactions. Finally, investigation of the value of the precipitate in the treatment of ragweed sensitive patients was undertaken.

METHOD

Glenny and Barr in 1931 determined in detail the conditions necessary for the optimum precipitation of diphtheria toxoid by alum. In 1932 M. L. Smith[5] investigated this problem further and added significant information, particularly concerning the influence of hydrogen ion concentration. These investigations served somewhat as a guide to the present chemical studies.

Preparation of Pollen Extract.—Ten grams of ragweed pollen (equal parts of giant and dwarf) were defatted with anhydrous ether in a Soxhlet apparatus, and the ether subsequently removed by vacuum

*From the Allergy Clinic, Cincinnati General Hospital, and Department of Medicine, College of Medicine, University of Cincinnati.

desiccation. The defatted pollen was then extracted with 200 c.c. of bicarbonate-saline extracting fluid (0.5 per cent sodium chloride, 0.275 per cent sodium bicarbonate, 1:10,000 merthiolate solution) for twenty-four hours. The extract was sterilized by filtration through a sterile Mandler filter. Total nitrogen and protein nitrogen determinations were made.

Preparation of Alum-Ragweed Precipitate.—One hundred and eighty c.c. of the sterile ragweed extract having a pH of 7.2 (potentiometric determination) was adjusted to a pH of 7.9 with sterile 2 per cent sodium hydroxide solution. To the adjusted pollen extract, 20 c.c. of sterile (by filtration) 10 per cent aluminum potassium sulphate was added very slowly with constant agitation to give a final concentration of 1 per cent. A fine flocculent precipitate formed at once and slowly settled out on standing. After the addition of alum solution the pH dropped to 6.2. This mixture was allowed to stand for twenty-four hours at 10° C. and then centrifuged. The supernatant liquid was siphoned off aseptically and physiologic saline was added to the precipitate to make the volume 180 c.c. The mixture was again centrifuged and the supernatant liquid once more removed. This washing was repeated, and the precipitate then suspended in 180 c.c. of physiologic saline solution (the original volume) and merthiolate was added as a preservative (1:10,000).

The suspension was used in this form in all the following animal and clinical studies. Where further dilutions were required, these were made with physiologic saline. Total nitrogen and protein nitrogen determinations by the Kjeldahl method were made and are recorded in Table I. (For nitrogen determinations the precipitate was dissolved in 10 per cent sodium citrate solution.)

TABLE I

NITROGEN DETERMINATIONS

PRODUCT	TOTAL NITROGEN (MG. PER C.C.)	PROTEIN NITROGEN (MG. PER C.C.)
Saline extract	0.530	0.219
Alum-ragweed precipitate	0.124	0.122
Supernatant liquid	0.250	0.210
First washing	0.042	None
Second washing	0.027	None
Supernatant liquid after suspension left standing three months	0.072	None

Comment.—Potassium alum was employed as the precipitating reagent, and the required volume was always added in the form of a 10 per cent aqueous solution. The concentration of alum was not varied in these chemical studies; i.e., in each case the amount used was calculated to give a final concentration of 1 per cent alum after all reagents had been added. This value of 1 per cent was arbitrarily chosen. The use of alum concentrations over 1 per cent has not as yet been investigated.

Protein nitrogen determinations done on the supernatant fluid; taken from a suspension of alum-ragweed precipitate that was allowed to stand at room temperature for three months, revealed no determinable protein nitrogen. This indicates that alum-ragweed precipitate is relatively stable. In preparing final suspensions of the precipitate, physiologic saline may, of course, be added up to any desired volume. By reducing the quantity of saline used, high concentrations of the precipitate can be obtained.

The mechanism of precipitation of ragweed by alum is assumed to be one of adsorption; that is, when alum is added in the presence of alkali, aluminum hydroxide, which forms as a colloidal precipitate, adsorbs ragweed protein from solution. The alternate possibility is that the precipitate is a chemical combination between the alum and ragweed to form an insoluble chemical compound. M. L. Smith[5] favors the adsorption hypothesis in alum precipitation of diphtheria toxoid and offers convincing evidence. The following additional observations are presented to support this hypothesis in the case of alum precipitation of ragweed. The addition of alum in varying concentrations to ragweed extracted in physiologic saline produced no precipitation. The presence of alkali was required before precipitation could be produced in alum-ragweed mixtures. The amount of ragweed precipitated from alum-ragweed mixtures was found to depend upon two factors: (1) the amount of aluminum hydroxide present (with a fixed concentration of alum, the amount of hydroxide precipitated varies in turn with the amount of alkali present); (2) the final pH of the mixture. The optimum pH for maximum ragweed precipitation was found to be about 5.0. This pH value approximates the isoelectric point of plant proteins, and at this point maximum adsorption occurs. Hence, though a smaller fraction of alum is effective as a precipitant at this more acid reaction, the increased ragweed precipitation must presumably be due to increased adsorption.

ANIMAL INVESTIGATION

A series of 12 guinea pigs were injected subcutaneously with 1 c.c. each of the suspension of alum ragweed precipitate (12,000 protein nitrogen units per cubic centimeter). An interval of twenty-two days followed. Three guinea pigs were injected intravenously with 0.25 c.c. each of aqueous ragweed extract (20,000 protein nitrogen units per cubic centimeter). These developed signs of definite anaphylactic shock but recovered. Each of the remaining nine guinea pigs received intravenously between 0.5 c.c. and 1.0 c.c. of the same aqueous ragweed extract. These died of typical anaphylactic shock confirmed by postmortem findings. It is evident from these observations that alum-ragweed precipitate is an effective sensitizing antigen. In contrast may be cited the recognized difficulties of sensitizing guinea pigs to ragweed with aqueous ragweed extracts.

Intracutaneous Reaction.—Intracutaneous injections of the undiluted suspension of alum-ragweed precipitate in amounts up to 0.2 c.c. in a series of normal subjects produced no local urticarial, erythematous, or pruritic response. In a series of ragweed sensitive patients, the activity of alum-ragweed precipitate and aqueous ragweed extract was compared by intracutaneous tests. The two extracts were of the same protein nitrogen concentration, and the intracutaneous injections were made in parallel rows on the upper arm with serial dilutions containing 1, 10, 100, and 1,000 protein nitrogen units per cubic centimeter. No differences between the two extracts were demonstrated. The character, dimensions, and appearance time of the resulting allergic wheals were the same in each case. It may be inferred, therefore, that the suspension of alum-ragweed precipitate contains active pollen elements similar to those of aqueous ragweed extract, and that these are liberated from both extracts at the same rate after intracutaneous injection.

Subcutaneous Injection.—No determinable reactions were noted in normal subjects on subcutaneous injection of the undiluted suspension of alum-ragweed precipitate in amounts up to 0.5 c.c.

To study the absorption of alum-ragweed precipitate after subcutaneous injection, five normal nonatopic adults who readily received passive transfer were selected. An area of skin in the upper arm was passively sensitized with 0.1 c.c. of the serum of a ragweed sensitive patient. Twenty-four hours later 0.1 c.c. of concentrated aqueous ragweed extract (25,000 protein units per cubic centimeter) was injected subcutaneously in the opposite arm. Positive wheal reactions appeared at the passive transfer sites within forty minutes. One week later passive transfer sites were again prepared on the upper arm of the same subjects. After twenty-four hours the concentrated alum-ragweed suspension was injected subcutaneously in the opposite arm of each, and the passive transfer site observed for activity. The results are presented in Table II.

TABLE II

ABSORPTION TIME OF ALUM-RAGWEED PRECIPITATE AFTER SUBCUTANEOUS INJECTION

CASE NO.	ALUM-RAG. PPT. (12,000 P.N.U./C.C.) AMOUNT INJECTED	APPEARANCE TIME OF EARLIEST REACTION	SIZE OF MAXIMUM REACTION AT PASSIVE TRANSFER SITE
1	0.5 c.c.	2 hours	2 plus
2	0.5 c.c.	2 hours	2 plus
3	0.5 c.c.	2 hours	4 plus
4	0.2 c.c.	3 hours	1 plus
5	0.2 c.c.	No reaction in 0 to 3 hours	

The appearance of positive reactions at the passive transfer sites indicates liberation and absorption of active ragweed fractions. Com-

parison of the appearance times with those for aqueous ragweed extracts reveals a definite delay in the absorption of these active fractions of alum-ragweed precipitate.

Further observations concerning absorption after subcutaneous injection were made during the time of administration of alum-ragweed precipitate to a group of ragweed sensitive patients. Ascending doses, beginning with 1, 10, or 100 protein units, were given in the usual routine method of preseasonal pollen therapy. A number of local reactions were observed at the site of inoculation. These appeared within one-half to twelve hours and were similar in appearance and duration to the local reactions found in control patients treated with aqueous pollen extracts. A number of constitutional reactions were observed. In two patients these occurred within one-half hour and in one, within two hours. These reactions were similar in all respects to those resulting from aqueous ragweed extracts. The appearance time of these local and systemic responses would indicate no appreciable delay in the release of active pollen elements.

Treatment of Ragweed Sensitive Patients.—Since alum-ragweed precipitate was a new and untried pollen antigen, a plan of therapeutic

TABLE III

PRESEASONAL TREATMENT OF RAGWEED SENSITIVE PATIENTS WITH ALUM-RAGWEED PRECIPITATE

CASE NO.[1]	AGE	DURATION	TYPE[2]	MAXIMUM DOSE OF A.-RAG. P. EXT.[3]	METHOD OF ADMINISTRATION[4]	RESULTS
1	42	17 years	H	0.10 c.c. conc.—1,200 P.U.	I	Poor
2	24	3 years	H	0.05 c.c. conc.— 600 P.U.	I	Poor
3	59	4 years	H & A	0.10 c.c. conc.—1,200 P.U.	I	Good
4	38	9 years	H & A	0.05 c.c. of 1:10—60 P.U.	I	Good
5	14	2 years	H	0.10 c.c. conc.—1,200 P.U.	I	Good
6	62	18 years	H & A	0.20 c.c. conc.—2,400 P.U.	S	Fair
7	37	3 years	H & A	0.20 c.c. conc.—2,400 P.U.	S	Fair
8	52	10 years	H & A	0.05 c.c. conc.— 600 P.U.	I	Poor
9	12	4 years	H & A	0.05 c.c. conc.— 600 P.U.	I	Good
10	38	18 years	H & A	0.10 c.c. conc.—1,200 P.U.	S	Poor
11	33	4 years	H & A	0.05 c.c. conc.— 600 P.U.	I	Good
12	74	15 years	H & A	0.05 c.c. 1:10— 60 P.U.	I	Poor
13	48	24 years	H & A	0.05 c.c. conc.— 600 P.U.	I	Poor
14	20	9 years	H & A	0.15 c.c. conc.—1,800 P.U.	S	Fair
15	60	30 years	H & A	0.50 c.c. conc.—6,000 P.U.	S	Good
16	62	30 years	H	0.30 c.c. conc.—3,600 P.U.	S	Good
17	43	3 years	H & A	0.05 c.c. 1:10— 60 P.U.	I	Poor
18	47	15 years	H	0.20 c.c. 1:10— 240 P.U.	I	Good
19	24	14 years	H	0.20 c.c. conc.—2,400 P.U.	S	Fair
20	20	5 years	H	0.20 c.c. conc.—2,400 P.U.	S	Poor
21	48	3 years	H & A	0.10 c.c. conc.—1,200 P.U.	I	Fair
22	50	4 years	H	0.05 c.c. conc.— 600 P.U.	I	Poor
23	35	8 years	H	0.30 c.c. conc.—3,600 P.U.	S	Good
24	11	4 years	H	0.20 c.c. conc.—2,400 P.U.	S	Good

[1]Cases 3, 13, and 19 were treated in 1935.

[2]Type: H—Hay Fever. H. & A—Hay Fever and Asthma.

[3]A.-Rag. P. Ext.—Alum-Ragweed Precipitate Suspension (12,000 protein nitrogen units per cubic centimeter). P. U.—Protein Nitrogen Units.

[4]Method of Administration: I—Intracutaneous. S—Subcutaneous.

administration had to be arbitrarily chosen. The plan selected was that of the routine method of preseasonal pollen therapy. Twenty-four patients of proved clinical ragweed sensitivity were given a series of injections of the suspension of alum-ragweed precipitate in ascending doses. Beginning with 1, 10, or more units, as was indicated by the sensitivity of the individual patient, the material was administrated to the various patients in increasing amounts at four- to seven-day intervals. Different maximum doses were given to the various patients, the maximum varying between 200 and 5,000 protein nitrogen units. A number of the patients received their more concentrated doses intradermally. The results of treatments are recorded in Table III.

Comment.—The results of treatment with the alum-ragweed precipitate may be summarized as follows: 42 per cent obtained good results; 21 per cent obtained fair results; and 37 per cent obtained poor results. A series of 50 control patients treated preseasonally in 1936 with aqueous ragweed extract in maximum tolerance doses showed these results: 60 per cent good; 18 per cent fair; and 22 per cent poor. As is evident the series treated with alum-ragweed precipitate obtained comparatively less satisfactory relief. Intracutaneous injections yielded no better results than subcutaneous administration, and were frequently followed by small central areas of slough. Since there was no standard by which to select an optimum maximum dosage of the precipitate, this was purposefully varied within fairly wide limits. Patients who received the higher maximum doses had better results than those on lower maximum doses. The lower maximum doses (e. g., under 1,000 protein nitrogen units) received by a number of patients were probably inadequate, and this may account in part for the inferior results obtained in the series as a whole.

SUMMARY

1. Alum-ragweed precipitate is an alum-modified ragweed extract. The method of its preparation is described.

2. Alum-ragweed precipitate is an effective antigen for sensitizing guinea pigs to ragweed, which confirms the work of previous authors.

3. Local and systemic reactions from intracutaneous and subcutaneous injections of alum-ragweed precipitate in ragweed sensitive patients are similar to those produced by equal protein nitrogen concentrations of aqueous ragweed extracts.

4. A slight delay in the absorption of the active pollen fractions of alum-ragweed precipitate as compared to aqueous ragweed extracts, was noted following subcutaneous injections in a series of normal adults.

5. The preseasonal treatment of a series of 24 ragweed sensitive patients with alum-ragweed precipitate is reported.

6. The active ragweed components of alum-ragweed precipitate are apparently identical to those of aqueous ragweed extract.

7. Further investigations are indicated, particularly: (a) variations in the chemical preparation of alum-ragweed precipitate, using greater concentrations of alum than 1 per cent; (b) variations in the methods of therapeutic administration.

The authors wish to express their indebtedness to the Wm. S. Merrell Company for their assistance with the chemical investigations, and to the Christ Hospital, Cincinnati, Ohio, for their assistance with the animal investigations.

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STUDIES IN THE PREPARATION OF POLLEN EXTRACTS*

I. Filtration by Carbon Dioxide Pressure

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IN THE extraction of pollens and house dust, Coca[1] recommended the use of "alkaline fluid" in preference to "buffered saline fluid" because extracts prepared of the latter were found to deteriorate considerably within a few months. When the alkaline fluid was employed, only a relatively slight deterioration of the excitant occurred. Working with similar preparations, Milford[2] observed that keeping house dust extract continuously provided with a slight excess of carbon dioxide was an important factor in preserving the specific activity of the extract, when it was being concentrated by fanning.

In allergy laboratories where pollen extracts are prepared with the alkaline extracting fluid as prescribed by Coca, and then filtered through a Seitz or Berkefeld filter by means of suction, one unsatisfactory result occurs. It is the general experience that, although a perfectly clear solution is introduced into the filter, the filtrate frequently returns showing precipitation and containing sediment. Up to the present time the only way to overcome the use of frothy pollen extract was to allow the preparation to stand until the flakes settled to the bottom, then to decant off the clear solution for use. This is a tedious procedure entailing possible contamination and loss of ingredient, and with it, loss of the specific excitant activity of the extract.[3]

We determined that this precipitation and sedimentation in the solution was caused by the withdrawal of carbon dioxide from the alkaline extracting fluid in the process of the suction filtration. When carbon dioxide was experimentally passed through a frothy solution, it promptly became clear. On the other hand, when carbon dioxide was withdrawn, a frothy cloudy solution again resulted. We, therefore, recommend filtration by means of carbon dioxide pressure rather than suction, for by the use of this method the solutions are always clear.

DESCRIPTION OF APPARATUS

A tank of carbon dioxide, to which is attached a reducing valve and which is equipped with a gauge to control the supply of the gas under pressure, is connected by fittings to a Seitz filter under pressure. It was found that in filtration a supply of ten to twenty pounds of pressure is necessary for the production of a clear filtrate. By means of multiple

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connections attached to the tank, it is possible to filter into a number of flasks at the same time, according to requirements, but with a corresponding regulated increase in pressure. The rapidity of filtration is directly dependent upon the pressure released.

Since it is evident that the more important factor in the suggested method is the use of positive pressure behind the fluid (in order to prevent the loss of CO_2, which occurs when the filtered fluid is subject to a negative pressure), our object could have been obtained equally well if pressure was made with air instead of with carbon dioxide.

CONCLUSION

The precipitation and sedimentation in pollen and other allergenic extracts which followed vacuum filtration were found to be due to the withdrawal of carbon dioxide during this suction process. Pollen extracts can be rendered permanently clear by filtration through a Seitz or Berkefeld filter under pressure of carbon dioxide or air. The use of pressure of this kind eliminates loss of the gas content which occurs during vacuum filtration.

Filtration under pressure of carbon dioxide or air is recommended for use to prevent: (1) loss of free and some combined carbon dioxide in the extract; (2) sedimentation and precipitation; and (3) loss of specific excitant content. Further work is being done to determine the amount of specific activity lost in the sediment resulting from vacuum filtration.

NOTE: "Buffered saline fluid" is an extracting solution originally recommended by Coca and commonly used for extraction. The two solutions of which it is composed, are kept in concentrated forms, namely:

1. NaCl	50.00 grams	2. Carbolic acid	4%
KH_2PO_4	3.63 grams		
Na_2HPO_4	14.31 grams		

A mixture of equal parts of these two stock solutions is diluted with 4 parts of distilled water.

The "alkaline solution" is composed of:

NaCl	0.5 %
$NaHCO_3$	0.275%
Phenol	0.4 %

If the fluid is alkaline to phenolphthalein, carbon dioxide is passed through it until it remains colorless when tested with that indicator. This solution is then kept ready for use in tightly stoppered bottles.

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ON THE IMMUNOLOGIC RELATIONSHIP BETWEEN GRASS POLLEN AND SEED*

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IT IS a well-known phenomenon that individuals suffering from grass pollen hay fever are allergic to many different grass pollens. It was even shown that grass hay fever subjects who had never been in contact with Bermuda grass[1] or *Chacturus fasciculatus,* an exotic species,[2] gave positive reactions to these grasses. Furthermore, it is frequently possible to desensitize a grass hay fever patient showing multiple hypersensitivity by using a single grass pollen extract (Coca). This presumably could not be achieved if the grass pollen allergens were strictly specific.

Although these observations show that there is no strict specificity among the pollens of the various grasses, this lack of specificity does not transgress the line of the family. Petow and I[3] had the opportunity of testing a large number of Europeans suffering from grass hay fever. Although all of these patients gave positive skin reactions to the grass pollens, not one of them reacted to ragweed pollen with which they had had no contact.

In earlier work on the chemical nature of pollen allergens,[4] I frequently found that guinea pigs which were sensitized to a certain grass pollen extract, would react nonspecifically to another grass pollen extract. However, the animals only rarely reacted to unrelated allergens; e.g., feather extracts.

These observations suggest that although the various grass pollen allergens are not strictly specific, they are, nevertheless, closely related to one another.

Since Wells and Osborne[5] have shown that there is an immunologic relationship between the antigens of various plant seeds, the question arose whether there is a relationship between the antigens of the pollens and seeds of the same plant. The botanist Mez believes that "all living cells of the same plant show a similarity of their reactions."

In sensitization experiments on guinea pigs,[6] I have shown that there is no relationship between the pollen and seed antigens of *Dactylis glomerata.* Skin tests upon individuals suffering from hay fever demonstrated that there is no relationship between the pollen and seed antigens of *Dactylis glomerata, phleum pratense* and *Alopecurus.*

Skin tests and sensitization experiments with rye seed extracts suggested that these extracts contain irritating substances which can cause nonspecific reactions.

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I therefore repeated the work with rye pollen and rye seed extracts on a group of patients, and enlarged the number of grasses by testing with pollen and seed extracts of timothy and orchard grass.

The extracts were prepared by first treating the pollens or ground seeds for fifteen minutes with ether. The ether was decanted, and the pollens or seeds were then extracted with 1 per cent sodium chloride solution (containing 0.3 per cent phenol)—first in a shaking machine for one hour, and then overnight in the ice box. The extraction fluid was filtered first through paper and then through a Berkefeld filter. The extracts were finally tested for sterility.

The nitrogen content of the pollen extracts ranged from 0.12 to 0.23 mg. per c.c., of the seed extracts from 0.19 to 0.43 mg. per c.c.

The extracts were applied to skin abrasions made on the patient's forearms with a Pirquet borer.

The experiments were carried out on 12 patients who, at some previous time, had shown positive skin reactions to timothy pollen extracts. Seven of these patients were refractive to all of the extracts used, 5 gave

TABLE I

PATIENT	TIMOTHY		ORCHARD GRASS		RYE		
	POLLEN	SEED	POLLEN	SEED	POLLEN	(SPRING) SEED	(WINTER) SEED
O. D. ♂	++++	0	+++	0	+++	0	0
T. K. ♀	++	0	+++	0	±	0	0
A. G. ♀	++	0	++	0	0	0	0
B. E. ♀	++++	0	++	0	+	0	0
S. H. ♀	++++	0	++	0	0	0	0

the results shown in Table I. These patients showed marked reactions to the pollens of timothy, orchard grass, and rye, but were not sensitive to the corresponding seeds.

CONCLUSIONS

Although a close immunologic relationship between the pollens of different grasses may be assumed, it has been shown in the foregoing and in earlier experiments that there is no immunologic relationship between the pollens and seeds of the same plant, in spite of their close biological relationship.

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THE INTERRUPTION OF THE ASTHMATIC CRISIS BY TRIBROMETHANOL (AVERTIN)*†

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IN THE past few years extensive investigations have resulted in a fairly uniform and adequate treatment of the usual asthmatic case. However, one is often confronted with a patient who exhibits constant and intense dyspnea, which is not relieved by the generally recognized methods of treatment, and in spite of employing the drugs normally considered efficacious in relieving the asthmatic attacks, an alarming crisis ensues which often leads to death.

The mechanism of this asthmatic crisis, which is referred to as *status asthmaticus* or intractable asthma, is still obscure. It is believed[1] to be caused by the mechanical effect of the sudden accumulation of a large quantity of very viscid secretion, similar to that seen in postoperative or posttraumatic atelectasis. Some, if not all, of the following factors condition the production of this asthmatic crisis:[2] "(1) an overdose of the allergen to the shock tissues of the lung; (2) a simultaneous multiple involvement of shock tissues; the combined allergic shock from several sources is so great that the body cannot recover from the induced effect; (3) an idiosyncrasy may be present to the drug used, that is an exaggerated or retarded physiologic response, making it extremely difficult to judge the optimum dose; (4) an added allergic shock in regard to a sensitivity to the drugs which ordinarily are beneficial."

The clinical picture presented is one of severe collapse with constant dyspnea to the point of exhaustion, and epinephrine, the usual aid, fails to be effective. Where the stubborn symptoms are due to a severe involvement of the paranasal sinuses, evacuation of the pus will frequently check the attack. Often the simple expedient of changing the patient's environment, such as hospitalization in a dust-free room, with or without the administration of a 10 per cent dextrose solution intravenously, will stop the attack in the true hypersensitive type. Intravenous sodium iodide is advocated by some authorities, and the use of the oxygen tent is at times helpful. When these and other well-recognized methods prove ineffectual and the situation becomes alarming, morphine is often resorted to in desperation, which may hasten the fatal outcome.[3]

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Some of the other methods that have been advocated to arrest an asthmatic crisis are: the inhalation of carbon dioxide,[4] or helium and oxygen;[5] x-ray therapy;[6] high frequency irradiation of the cervical sympathetics;[7] dorsal sympathectomy;[8] and colonic administration of ether in oil.[9]

In a series of asthmatic patients upon whom various types of sinus surgery were performed with avertin employed as a basal anesthetic, most noticeable was the ease with which the patient accepted the procedure, and the freedom from asthma which developed following the operation, to a degree greater than that usual after other types of anesthetic. The patient was completely relaxed, and the recovery was unaccompanied by any severe reactions. Since it is generally agreed that in order to interrupt an asthmatic crisis sedation is beneficial, it seemed that narcosis induced by avertin might be effective in arresting this difficult and intractable condition.

This deduction was confirmed by using avertin as a last resort, after the usual procedures had failed on a number of adult patients admitted as emergency patients to the Metropolitan Hospital in persistent and apparently intractable paroxysms of asthma. Tribromethanol in amylene hydrate (avertin fluid) was slowly injected rectally, using a funnel or a syringe with a male catheter. The dose was always less than that recommended for surgical procedures. From 50 mg. to 70 mg. of the drug were used per kilo. of body weight. The lower figure was seldom sufficient to quiet the patient; 60 mg. usually proved adequate. Muscular relaxation usually occurred within ten to twenty minutes, but at times one hour was required because of delayed absorption, due to either the presence of a fecal impaction or the previous administration of some drug which had excessively stimulated the patient, thus necessitating longer sedation. The reflexes gradually diminished, the labored breathing subsided, and the patient eased into a natural sleep. There was a temporary drop in blood pressure, averaging 10 systolic and 5 diastolic.

The patients slept from one to six hours and upon awakening were able to breathe without effort, experiencing none of the after-effects observed upon the use of other anesthetics. Nausea and vomiting were absent. Some patients complained of slight frontal headache, and some expectorated large quantities of mucus. In the cases observed there was no irritation of the rectum. Occasionally a patient would wake up after one hour, answer questions while in the stuporous state, then doze off again for several hours. It was the usual thing for the patient to express gratification at being able to sleep. Some of them had not slept well for days or weeks. Nervousness and excitement were absent.

Once the crisis had been overcome, patients frequently were free from asthma for days and even weeks and required no further urgent treatment. In others a troublesome cough, from the associated bronchitis, would remain, requiring medication. Those who experienced asthma subsequently were relieved by the usual helpful drugs. It was especially noted that the refractoriness to epinephrine was lost. Once the urgency had passed, the usual allergic factors as well as the focal infections were attended to.

Avertin was used successfully on adult asthmatic patients of the skin-positive and of the skin-negative or infective groups. In a series of 25 cases the proper administration of avertin was highly effective in arresting asthmatic crises. No untoward results were discovered in asthmatic patients in whom it was employed. At times its use proved to be the deciding factor between a favorable and a fatal outcome.

The study of the use of avertin in severe asthma is being continued.

The following cases are typical of the behavior of avertin in interrupting an asthmatic crisis:

CASE 1.—M. M., female, aged twenty-eight years, was admitted to the hospital on March 26, 1936, with a severe attack of asthma which was not relieved by epinephrine or ephedrine. She had been suffering from asthma for the past fifteen years with no seasonal variations. The attacks were usually paroxysmal in character and nonenvironmental. She had attended several clinics where skin tests were performed and treatment instituted. There were no associated allergic conditions such as hay fever, urticaria, eczema or migraine, and no history of allergy in the family. She had typhoid at age of twelve. She slept on silk floss pillows; used no cosmetics; had no pets at home; and had no idiosyncrasy for any drug or food.

Physical examination showed an emaciated woman, weighing 102 pounds, in constant dyspnea. Except for the typical asthmatic wheezing and breath sounds over the lungs, there were no abnormal findings. The heart sounds were regular, of good quality, and no murmurs were present. Pulse was 90; temperature 100° F.; respiration 28; and blood pressure 120/72. X-ray of chest and sinuses was negative. Urine and blood analysis were normal, and the Wassermann reaction negative.

The following medications were given repeatedly without relief: epinephrine; ephedrine; sodium amytal; paraldehyde; concentrated hydrochloric acid in distilled water; infusion of 10 per cent glucose solution; carbon dioxide and oxygen; morphine sulphate gr. $\frac{1}{6}$ with scopolamine hydrobromide gr. $\frac{1}{150}$.

After three days of constant dyspnea the situation became alarming and the patient was completely exhausted. Temperature was 101° F.; pulse 96; respiration 28; and blood pressure 124/76.

On March 29, 1936, 2 c.c. of avertin fluid in 80 c.c. of distilled water (43 mg. per kilo.) were slowly injected rectally through a funnel. After one-half hour, there was slight muscular relaxation, the patient felt more at ease but the wheezing continued. The dosage of avertin fluid was then increased to 60 mg. per kilo. body weight. Within ten minutes the patient became drowsy, the reflexes diminished, and she eased into a natural sleep. The blood pressure at this time was 116/70.

She awoke after four hours without any evidence of dyspnea or any postanesthetic reactions, and remained free from asthma for three days. When the wheezing recurred she responded to the usual symptomatic medication such as ephedrine and epinephrine.

Intradermal tests, performed after the crisis had been arrested, gave positive reactions to orris, dust, feathers, goat epithelium, tobacco, insecticide, wool, pork, pepper, and tomato.

She remained in the hospital for two weeks and was then referred to the asthma clinic for further treatment.

CASE 2.—W. M., male, aged twenty-two years, was admitted to the hospital on December 19, 1936, in an acute asthmatic attack. He gave a history of frequent similar occurrences which usually followed a "cold" and which were relieved by oral administration of ephedrine. He stated that six months previously a radical operation was performed on his sinuses with no improvement in his asthma. He did not suffer from hay fever, eczema, urticaria, or migraine. There was no history of allergy in the family. Intradermal tests had not been performed.

Physical examination showed an undernourished young man weighing 103 pounds, in a severe attack of dyspnea. There were nasal crusting and coryza. Sonorous and sibilant râles were heard over the entire lung area. The heart sounds were regular and of good quality. Pulse was 80; temperature 99° F.; respiration 26; and blood pressure 100/80. Urine and blood chemistry were normal.

Repeated injections of epinephrine (5 minims every four hours—6 doses); two doses of ephedrine sulphate gr. ⅜ and allonal gr. 2 by mouth; inhalation of carbon dioxide and oxygen failed to relieve the asthmatic attack.

After twenty-four hours of uncontrollable asthma, 3.3 c.c. of avertin fluid in 132 c.c. of distilled water (70 mg. per kilo.) were slowly administered rectally through a funnel. It required six minutes for the injection of the entire solution. After twelve minutes the labored breathing subsided, the reflexes diminished, and the patient gradually fell asleep. He awoke after one hour, answered questions lethargically, mumbling gratification at being able to sleep and then dozed off again.

On awakening six hours later he complained of a slight frontal headache. He was free from asthma during the remainder of his stay, ten days at the hospital. He was then referred to the asthma clinic for intradermal testing and treatment.

CASE 3.—G. S., female, aged thirty-eight years, was admitted to the hospital on December 31, 1936, in a semistuporous state with a severe asthmatic attack which had persisted for six days prior to admission, and for which she had received large doses of epinephrine, ephedrine, and amytal, without relief. No further history was obtained, due to the patient's condition.

Physical examination showed an emaciated middle-aged woman weighing 110 pounds, in extreme dyspnea and cyanosis. Numerous small polypi projected from the right nasal mucosa. Sonorous râles were heard over the entire lung area, except the lower right base posteriorly where there were distant breath sounds and dullness on percussion. Heart sounds were rapid, regular, and no murmurs were present. The abdomen was markedly distended. Temperature was 102.4° F.; pulse 140; respiration 28; and blood pressure 152/106.

Within a period of twelve hours the patient received, without any result, injections of 5 minims of epinephrine every three hours (3 doses); ephedrine sulphate grain ⅜ and amytal grains two by mouth (2 doses); sodium iodide (1 gram in 20 c.c. of water) intravenously, infusion of 500 c.c. of a 10 per cent glucose solution, inhalation of carbon dioxide and oxygen and morphine sulphate gr. ⅙ and atropine sulphate gr. $\frac{1}{150}$ hypodermically.

At this time, the patient was extremely exhausted and the dyspnea was intense.

Three c.c. of avertin fluid in 120 c.c. of distilled water (60 mg. per kilo.) were instilled slowly into the rectum through a funnel. The absorption was delayed due to marked fecal obstruction. After one-half hour the labored breathing began

to subside and the patient relaxed. The blood pressure at this time was 138/96. A quiet normal sleep occurred in one hour.

The patient awoke after four hours and expectorated a large quantity of mucus. She complained of dryness of her mouth. There was slight wheezing over the lung area with numerous moist râles at the right base posteriorly. The wheezing was controlled with 0.2 c.c. of epinephrine given intracutaneously every four hours.

The patient showed a temperature ranging from 100° F. to 102° F. for a period of six days. X-ray examination disclosed peribronchial infiltration, bronchiectasis of the right base, and pansinusitis.

Intradermal tests performed with the inhalants and foods were entirely negative.

The patient was referred for treatment of her sinus and lung infections.

CASE 4.—E. L., male, aged forty-five years, was admitted to the hospital January 20, 1937, with severe shortness of breath which had persisted for one week. There was a history of frequent colds as a child. His asthma began six years previously following an attack of pneumonia, complicated by empyema for which a thoracotomy had been performed. The asthma occurred only in the winter and during changes in weather, lasting from one to three weeks with expectoration of thick tenacious sputum. Injections of epinephrine usually gave him temporary relief, but were of no help in his present paroxysm. There was no history of allergy in the family. For the past nineteen years he had been employed as a chauffeur, driving a truck and collecting ashes. He smoked two packages of cigarets daily, slept on feather pillows, and experienced a fullness in the epigastrium after eating white bread.

Physical examination showed an obese middle-aged man weighing 185 pounds, in severe dyspnea and orthopnea. There was slight ulceration of the hard palate, chest was emphysematous, tactile fremitus decreased, and hyperresonant on percussion. Sonorous râles were heard over both lung fields, moist râles over both bases, more marked on left side. Expiration was prolonged. Heart sounds were distant, regular, and no murmurs were heard. The abdomen was normal; the temperature 100° F.; pulse 96; respiration 26; and blood pressure 124/80. Urine and blood chemistry were normal, and the Wassermann negative. X-ray examination disclosed increased markings both lung fields; pleural thickening at the left lower lobe; and the cardiovascular shadow normal. Blood count R.B.C., 3,800,000; W.B.C., 8,600; Hb., 70 per cent; polys, 64 per cent; lymphocytes, 32 per cent; and eosinophiles, 4 per cent.

Continuous medication over a period of two days did not relieve the dyspnea. The patient complained of inability to sleep for the past week. Injections of 5 minims of epinephrine every ten minutes for 4 doses, then given every four hours, three grains of sodium alurate by mouth given four times during the two days, 15 drops of potassium iodide in water three times daily, one injection of a grain of codeine sulphate, one injection of ⅓ grain of pantopon, and the inhalation of carbon dioxide and oxygen all failed to arrest or even diminish the dyspnea.

These routine procedures being ineffectual, 5 c.c. of avertin fluid in 200 c.c. of distilled water (60 mg. per kilo.) were slowly administered rectally through a funnel. Absorption was slow but after twenty-five minutes the troubled breathing subsided, the patient relaxed, and the reflexes diminished. The blood pressure was 115/75. At this time the patient rose to a semirecumbent position, cleared his throat, and expectorated a large quantity of mucus on the bed. He did not appear to hear any questions asked of him, and when touched even gently, he showed his resentment by mumbling and recoiling from the touch. He then fell asleep and slept soundly for six hours.

He awoke with no indications of difficult breathing and rested comfortably in bed almost the entire day. He expressed pleasure at his first opportunity to sleep within a week. Ten minims of a saturated solution of sodium iodide in water three times a day were continued to help liquefy the mucus and allow for expectoration. No other medication was necessary.

Skin tests performed with the inhalants and foods were negative.

CASE 5.—M. A., female, aged thirty years, was admitted to the hospital on January 28, 1937, in a severe paroxysm of asthma which had persisted for sixteen hours in spite of frequent administrations of epinephrine and ephedrine. She had suffered from asthma for ten years. The attacks were nonseasonal, but occurred more frequently during the winter months. Skin tests had been performed and "injection treatments" given at a clinic which she had attended irregularly in the past four years. She did not suffer from hay fever, eczema, urticaria, or migraine. A son eight and one-half years of age had asthma. She slept on kapok pillows, used no cosmetics, and had no pets at home. Morphine injections administered on several occasions when she had experienced severe asthma had aggravated the asthma and "made her very sick." She avoided foods containing wheat upon the advice of a physician.

Physical examination showed a restless, apprehensive woman, weighing 126 pounds, in a severe paroxysm of dyspnea. The usual asthmatic sounds, short inspirations, and prolonged expirations with audible wheezing and occasional moist râles were all that could be elicited. The heart sounds were rapid, regular, and of fair quality. No murmurs were present. Temperature was 99.5° F.; pulse 104; respiration 24; and blood pressure 125/75.

The following medications were given without relief: 10 minims of epinephrine for 1 dose, then 5 minims every four hours (4 doses); 1/120 grain of atropine sulphate (1 dose); 3½ grains of sodium alurate (2 doses); a retention enema of 20 grains each of chloral hydrate and sodium bromide and continuous inhalation of carbon dioxide and oxygen. Injections of morphine were not attempted (apparently) because of the history of idiosyncrasy to this drug.

At 11 A.M., January 29, after thirty-four hours of persistent, uncontrollable dyspnea, the patient's condition became alarming. The eyes assumed a fixed hopeless stare, the lips became cyanotic, perspiration appeared on the face, and the breathing became spasmodic. The pulse was rapid and feeble. Avertin fluid was resorted to in a final attempt to interrupt the paroxysm in dose of 3.3 c.c. of avertin fluid in 126 c.c. of distilled water (60 mg. per kilo.) injected slowly into the rectum. Absorption was rapid. Fifteen minutes later, the labored breathing gradually subsided and the patient relaxed. The blood pressure at this time was 116/72. Her sleep was not profound. She would awake at intervals of an hour or two, toss about, attempt to arise, then doze off again. At 10:30 P.M. she awoke excitedly with slight wheezing. Reassurance was necessary to allay her fears, and 0.2 c.c. of epinephrine was injected intracutaneously to control the wheezing. The patient volunteered the information that she was normally highly excitable, and that during and following these asthmatic episodes her irritability increased. A teaspoonful of elixir alurate three times a day was prescribed.

The next morning, January 30, she began to expectorate a small quantity of mucus. The wheezing was slight and required no medication. Her anxiety dispelled, she ate the regular diet and conversed slowly and intelligently.

Intradermal tests gave positive reactions to dust, feathers, dog epithelium, kapok, tobacco, insecticide, wool, wheat, rice, pork, and pepper.

The writer is indebted to Dr. George H. Van Gilluwe and his staff of the Metropolitan Hospital for their skilled assistance in giving anesthesia.

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29 EAST NINTH STREET

THE HEART IN BRONCHIAL ASTHMA*

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ACCORDING to Michael and Rowe[1] there are now on record 49 cases of death caused by bronchial asthma in which pathologic and microscopic studies have been described. This report includes two cases of their own. The reader is referred to their very worth-while article for a good description of bronchial asthma, its symptoms, signs, and pathologic findings.

According to these authors, the heart in bronchial asthma is rarely abnormal on general physical examination. At autopsy, the gross findings in one case were negative, and in the other case there was slight paleness of musculature with consistency less firm than normal. On microscopic examination the musculature of this heart presented a very mild degeneration, or infiltration. The coronary vessels and aorta were normal. The microscopic examination of the second heart was entirely normal, as were also the pulmonary vessels.

These authors quote Kountz and Alexander[2] as having found, postmortem, mainly normal or only slightly abnormal hearts. However, others reporting autopsies of patients dying of asthma, mention cardiac changes, including dilatation of the right ventricle, cardiac enlargement, and right ventricular hypertrophy.

MacDonald[3] found right ventricular hypertrophy, fatty infiltration of myocardium, and patchy myocardial fibrosis in four of his eight cases, and endocardial sclerosis in three of his subjects.

Wright[4] found no hypertrophy and no pulmonary arteriosclerosis.

Fisher and Beck[5] report one case in which at autopsy the heart was found to be moderately hypertrophied and there was some dilatation in the conus area. There were three or four small, firm, yellowish-beaded nodules on the mitral valve leaflets. The *chorda tendineae* were somewhat thickened at the valvular end. The anterior papillary muscle was slightly hypertrophied. The cusps of the aortic valve were thickened, and at the base of each was an atheromatous plaque. The adjacent edges of the anterior and right posterior leaflets were adherent for a distance of 3 mm. The coronary arteries were essentially normal, with the exception of a few atheromatous plaques in the intima. On microscopic examination this heart showed an old endocarditis and hypertrophy of the right ventricle, probably wholly independent of the asthma.

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Murphy and Case[6] report a case in which the heart weighed 215 gm. The organ was normal in size, shape, and consistency. The valves showed no change, and the coronary arteries had only very small yellowish patches in the intima.

It was the opinion of Alexander that the reported hypertrophies were due to causes other than asthma, and that bronchial asthma diminishes cardiac output, thus sparing the myocardium.

Harkavy,[7] on the other hand, pointed out that spasmodic asthma with emphysema might produce right ventricular hypertrophy. He also felt that in chronic cases constant strain on the right heart is certain to bring about right-sided cardiac hypertrophy and insufficiency, and gives as his opinion that the patient dies of cardiac failure. In discussing the work of Michael and Rowe, Harkavy also states that he saw definite eosinophilic infiltration in the walls of the pulmonary arteries, leading to the conclusion that allergic reaction may occur not only in lung tissue but in the blood vessels themselves, and that the vascular system may be the seat of manifestations due to hypersensitiveness.

Vaughan, in discussing this article, states that a person suffering from cardiac valvular disease may have a superimposed bronchial asthma, and cardiac failure be the cause of death; also that the giving of digitalis may lead to fatal issue in bronchial asthma.

Unger[8] reports 74 cases with electrocardiographic, pulse, and blood pressure findings, from which he deduced that there is "definite damage or tendency toward damage to the heart in bronchial asthma, only 31 per cent being normal. The small percentage of perfectly normal tracings should make us try all the harder to see these cases early, before the complicating emphysema and bronchitis come on and the heart is damaged. The striking finding is the great frequency of a low R_1 and a high R_3." This, he thinks, must be considered as strongly suggesting that the heart is on its way toward right axis deviation, due to right heart strain.

Coca, Walzer, and Thommen,[9] in a most comprehensive discussion of cardiac and circulatory findings in asthma, and basing their opinions largely upon the investigations of Alexander, Luten, Kountz, and Harkavy, state: "On purely theoretical grounds the impression has generally prevailed that there is hypertrophy and dilatation of the right heart in bronchial asthma." However, they add, recent investigations have cast considerable doubt upon the validity of this impression and the premises upon which it is based, and that the heart "remained singularly free from injury after continuous bronchial asthma, despite the attendant emphysema." They conclude that the organ is considerably spared in asthma and that, despite the pallor, rapid small pulse, palpitation, fall in blood pressure, and cyanosis, the increased intrathoracic pressure really diminishes the cardiac intake and thus saves the heart.

Kountz, Alexander, and Prinzmetal[10] have more recently studied the effects of emphysema, such as follows bronchial asthma, on the heart. The process was studied both in human beings and experimentally in dogs, and in 19 dogs that survived the operation and later came to autopsy, it was found that eight hearts appeared essentially normal and eleven were pathologic. Of the latter, right ventricular dilatation was prominent in all. Others showed some hypertrophy of the right and left ventricles. They concluded that the heart is affected in the majority of patients with emphysema and that the lesion, cardiac hypertrophy with dilatation of the right ventricle, when advanced, may produce symptoms, but probably has no clinical reflection in its earlier stages. They are unable to explain the left ventricular hypertrophy, but believe that their experimental evidence indicates that the right ventricular hypertrophy and dilatation occurs chiefly in the earlier stage of emphysema when the lungs are in the process of distention, rather than later as generally believed.

In the nine cases in our series in which death occurred, six were examined postmortem with histopathologic studies, and in three cases permission for postmortem examinations was refused. Four cases had normal hearts. One had valvular heart disease, apparently unrelated to his asthma, but which undoubtedly caused symptoms, as shown by edema, passive congestion, etc. An adhesive pericarditis was found at autopsy in one case in which the heart was apparently otherwise normal. Of the three cases that did not come to autopsy all apparently died of bronchial asthma, and one had clinical and electrocardiographic findings of cardiac disease.

The hearts examined in these cases varied in weight from 275 to 375 gm. In three cases no pathologic conditions were found grossly or by microscopic examination. In one the lungs were adherent to the pericardium and the histologic study revealed dense fibrous adhesions obliterating the pericardial sac, but the heart itself was undamaged. In one case there was marked hypertrophy and dilatation of the right heart, a fibrotic myocardium, and moderate narrowing of the lumen of the coronary artery. In another case there was dilatation of the right ventricle, and acute congestion of the liver, spleen, and kidneys, and the myocardium contained a few scattered lymphocytes and polymorphonuclear neutrophilic leucocytes and occasional fibroblasts.

The clinical study is based on a review of the clinical findings in 84 cases of bronchial asthma.

The heart was found to be normal on clinical examination in 79 of the 84 cases. One patient had a mitral stenosis complicating his asthma, two had pericardial adhesions, two showed cardiac enlargement clinically, one of them accompanied by cyanosis and edema.

The blood pressure in this group was found to be normal in all but five cases. Three showed a hypertension with pressures of 170/100, 160/100, and 150/90, respectively, and two showed a hypotension with pressures of 90/60 and 94/75 respectively.

Roentgen ray examination of the chest was made in all of the cases, and in the majority teleroentgenograms were made so that the size of the heart could be determined accurately. A cardiothoracic ratio of 50 per cent or over was considered as evidence of cardiac enlargement. There were three cases in the entire group which showed a cardiothoracic index of over 50 per cent, being 51.7, 53, and 55 per cent, respectively. There were three which showed small hearts with cardiothoracic indices of 37, 33, and 32 per cent, respectively. All of the others were found to be within normal limits as to size, shape, and position.

Electrocardiograms were made on 56 of the 84 cases. Thirty-four (61 per cent) were found to be entirely normal. Eleven (20 per cent) showed definite evidence of myocardial involvement. Three of these, however, could be accounted for on the basis of organic cardiac disease—mitral stenosis, one; hypertension, one; and coronary disease, one. The electrocardiographic findings in these 11 cases were as follows: Delayed auriculoventricular conduction, two; arborization block, one; and negative T-waves, eight. One patient showed inversion of the T-waves in Leads II and III during the attack, and a normal electrocardiogram after the attack had subsided. Of the electrocardiograms with negative T-waves, inversion of the T-wave was present in Lead II and Lead III in five cases. This is noteworthy, as T-wave inversion in Leads II and III is indicative of right heart involvement.

Preponderance was noted in 11 (20 per cent) of the 56 electrocardiograms. Ten of these showed right ventricular preponderance and one left ventricular preponderance. The index of preponderance also was studied in this group. The formula $(R_1 + S_3) - (S_1 + R_3)$ was used to determine the index. An index of +15 was considered definite evidence of left ventricular preponderance, and an index of –12 was considered as definitely right preponderance. Of the 56 electrocardiograms, 44 showed a minus index and 12 showed a plus index. The average index of preponderance for the group was –5.5. This would indicate a definite tendency toward right axis deviation in this group.

A further study of the index of preponderance was made with relation to the duration of the asthma. It was found that in the group with asthma of less than 1 year's duration the index was –3.3; in the group with a duration of two to ten years the index was –5.2; while in the group with a duration of over ten years the index of preponderance was –6. It is noted, therefore, that the tendency to right axis deviation increased as the duration of the asthma increased.

It is also noted that in all of the cases which showed definite evidence of myocardial involvement, such as negative T-waves, delayed conduction, and arborization block, the duration of the asthma was ten years or more; and that in no case in which the asthma was under ten years in duration was there any evidence of definite myocardial involvement.

The fact that right ventricular preponderance was noted in 20 per cent of the cases, and that the index of preponderance showed a definite tendency to right axis deviation in the entire group; also that this tendency increased as the duration of the asthma increased, would indicate that asthma causes a definite strain on the right heart.

The finding of inversion of the T-waves in Leads II and III of the electrocardiogram in a majority of the cases showing negative T-waves, and also the fact that the findings denoting myocardial involvement were present only in the cases in which the duration of the asthma was ten years or over, would also indicate that there is a tendency to right heart involvement in bronchial asthma.

Our clinical findings would be in keeping, therefore, with the conclusions of Unger and with the recent experimental findings of Kountz, Alexander and Prinzmetal; and it appears, therefore, that there is definite evidence of right ventricular strain in bronchial asthma, with a tendency to myocardial involvement and heart muscle damage as the disease progresses and emphysema ensues.

SUMMARY

A study was made of the heart in 84 cases of bronchial asthma.

There were nine deaths in this group, and six cases came to autopsy.

From a pathologic standpoint the heart was not greatly involved in uncomplicated cases of bronchial asthma. In one patient dying of acute asphyxia there was found dilatation of the right heart. Two cases complicated by various degrees of emphysema, bronchiectasis and lung abscess showed hypertrophy, dilatation, and congestive heart failure.

Pathologic findings of these six autopsied cases are reported.

No clinical evidence of heart disease was found in the majority of cases.

Definite evidence of right ventricular strain with a tendency to myocardial involvement was noted in the electrocardiographic study.

It must be concluded, therefore, that the heart does not remain singularly free from injury in bronchial asthma, and that right ventricular strain with a tendency to myocardial involvement and heart muscle damage does occur as the disease progresses and emphysema ensues.

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TRIPLICATE DETERMINATIONS OF THE SUGAR TOLERANCE IN MILD AND SEVERE ASTHMA*

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THE search for some abnormality of physiology or anatomy which might explain why certain individuals have the capacity to develop a sensitiveness to foreign substances, constitutes the fundamental problem in clinical allergy. In November, 1935, Wilmer and his associates[1] presented a report of their observations which led to the rather startling conclusion that "the carbohydrate tolerance and metabolism are altered in the allergic state." The authors found that the sugar tolerance curve was lower in allergic than in normal individuals. In July, 1936, MacQuiddy, McIntyre, and Koser[2] published their findings that the blood sugar tolerance curves of 20 patients with asthma were quite the same as the curves shown by 21 normal control individuals. Evidently, there are discrepancies in the results of such studies. It occurred to us that if several curves were studied at different times in the same patient, they might show different results. Perhaps there is a variable difference between the curves obtained from capillary and those from venous blood. Perhaps the patients who use adrenalin in quantity might show marked variations in their capacity to utilize sugar. It seemed worth while to study the problem once more, but now with every effort to control the experimental methods.

In the present work, repeated sugar tolerance tests were carried out to study the variations in repeated tests, and also to compare the analyses of both the capillary and the venous blood sugar levels. For the study, 24 subjects were chosen from our Allergy Clinic: 13 females and 11 males, all between the ages of twenty-nine and fifty-nine, and most between thirty-five and forty-five. Four of these subjects were patients suffering from asthma in severe form which required them to take frequent doses of adrenalin. These four "adrenalin users" will be discussed separately.

All patients were ambulatory and were in the habit of coming to the clinic each week for treatment. This treatment was always given at the conclusion of the sugar tolerance tests so as to minimize the effect of the treatment on the test. Prior to the first test, each subject was instructed to have his usual mixed diet the day before the test, and to make a com-

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plete written record of this diet. At the time of the first test, this record was copied into the notes and then returned to the individual with instructions to repeat the identical diet on the day preceding the subsequent tests. We believe that these dietary instructions were followed. All subjects were cautioned to avoid unusual excitement during the interval between tests and especially during the day before the test. During the tests, the patients were kept at rest and free from excitement.

The time interval between tests in all cases was seven days. Each test was carried out in the morning, after a twelve- to fifteen-hour fast. The preliminary blood samples were drawn and then the patients were given by mouth, 100 grams of glucose dissolved in 200 c.c. of tap water. Blood samples were taken while the subjects were fasting, and then again, at one-half-hour, one-hour, two-hour, and three-hour intervals, after the glucose ingestion. Samples of venous blood were drawn from the arm veins and at as nearly the same time as possible, capillary samples were obtained from the finger pads. Small (1.00 c.c.) all glass tuberculin syringes with a 24- or 26-gauge hypodermic needle were used for drawing the venous samples, and a small spear head lance was used for the capillary specimens. For analysis, 0.1 c.c. of each type of blood was used, and the blood sugar determinations were carried out by the method of Folin.[3] Each analysis was made in duplicate, and the data represent the average of two determinations in each case. That is to say, to study one test on each patient, 20 chemical analyses were made on ten blood samples.

The results of these analyses are presented in Table I as well as in the curves appearing in the text figures. The average venous blood sugar levels of the first tolerance test in our 20 patients have been plotted for comparison with the similar composite curves of other investigators—Lennox,[4] Gray,[5] Covett and Seljeskog.[6] These curves are not shown here, but it can be stated that the average sugar tolerance curve as plotted for our 20 allergic subjects lies quite in the middle of the range of the tolerance curve observed for nondiabetic and supposedly nonallergic individuals.

The individual sugar tolerance curves, each made on three separate occasions in 10 of our allergic patients, are shown in Fig. 1. Patients J. S., S. S., and G. C. had asthma; the others had hay fever. In the figures the lower solid line represents the venous blood determinations, while the upper dotted line shows the capillary blood values. As the figures and tables show, the fasting blood sugar values are remarkably uniform, the grand average being 94 mg. per 100 c.c. (Table I).

Our figures for the fasting blood sugar level in hay fever and asthma are, therefore, in agreement with the studies of Ramirez and others[7] who found normal fasting blood sugar values in 40 allergic individuals.

They do not agree with the figures of Malone[8] or of Black,[9] both of whom reported that the fasting blood sugar levels in allergic individuals were lower than normal.

A study of the curves on Fig. 1 shows that the variations among the three separate observations in each individual subject are slight. The

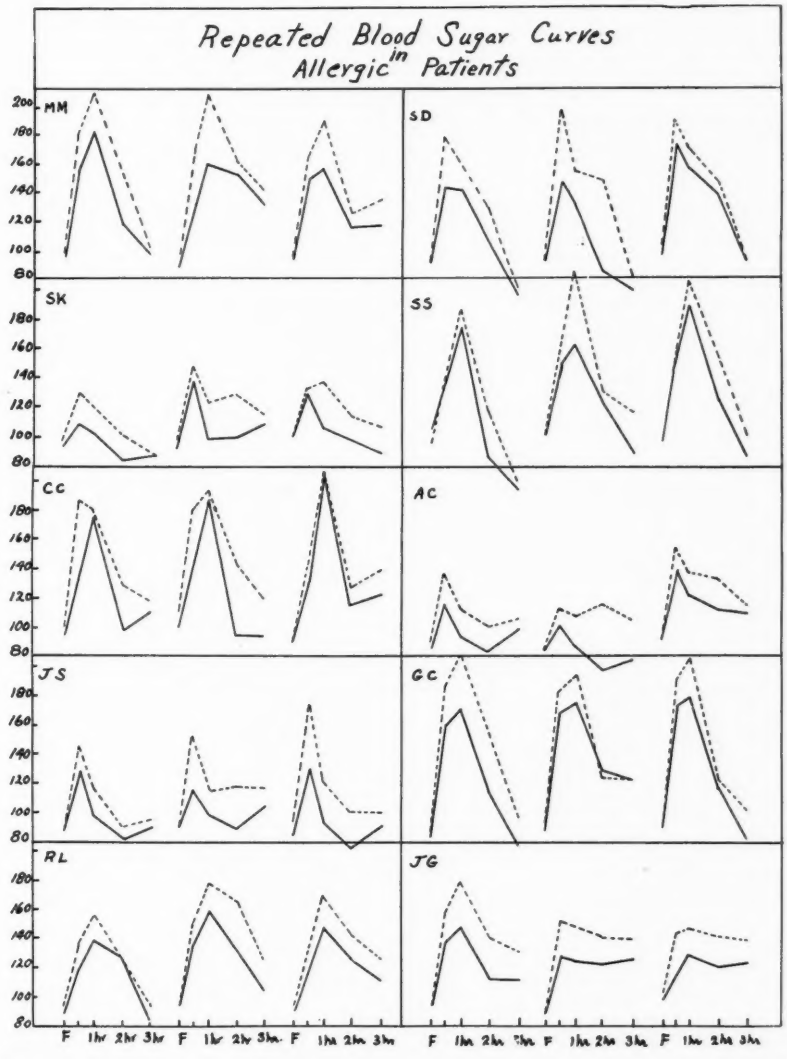

Fig. 1.—Individual sugar tolerance curves as determined in 10 allergic patients, showing the results of determinations repeated at weekly intervals, and giving the comparison of the findings in venous blood (solid line) and capillary blood (dotted line).

three curves of the capillary bloods are almost identical, while the venous values show only a slight tendency to increase with each succeeding test.

The average peak and postpeak values show a slight progressive increase from the initial to the third test values, and with each repetition,

TABLE I

BLOOD SUGAR VALUES

		CUTANEOUS BLOOD					VENOUS BLOOD					CUT.-VEN. DIFFERENCE				
	DATE, 1936	F.*	0.5 HR.	1 HR.	2 HR.	3 HR.	F.*	0.5 HR.	1 HR.	2 HR.	3 HR.	F.*	0.5 HR.	1 HR.	2 HR.	3 HR.
R. L.	7/ 9	94	138†	**156**	125	95	90	120	**140**	125	85	4	18	16	0	10
	7/16	95	157	**180**	166	127	95	136	**161**	134	105	0	15	21	32	22
	7/23	96	136	**171**	144	127	93	114	**149**	127	112	3	18	22	17	15
F. L.	7/ 9	89	**123**	92	88	90	88	**98**	94	76	84	1	25	-2	11	6
	7/16	83	**139**	114	122	110	82	**113**	105	107	95	1	26	9	15	15
	7/23	90	**126**	117	116	116	90	**127**	103	88	86	0	-1	14	28	30
M. M.	7/10	94	178	**206**	145	95	96	152	**179**	115	100	2	26	27	30	-5
	7/17	96	164	**206**	160	140	87	130	**157**	150	131	11	34	49	10	11
	7/24	95	161	**188**	124	133	92	144	**153**	114	115	3	17	35	10	18
S. D.	7/10	91	**177**	156	127	73	90	**141**	139	106	68	1	36	23	21	5
	7/17	94	**196**	152	146	82	93	**146**	130	85	72	1	50	32	61	10
	7/24	96	**189**	169	145	91	103	**171**	154	139	91	-7	18	15	6	0
F. M.	7/10	91	**164**	156	120	115	90	144	**160**	152	72	1	20	-4	-32	43
	7/17	114	152	**203**	114	124	109	134	**166**	109	105	5	22	37	5	19
	7/24	91	**151**	133	115	74	84	119	**119**	89	73	7	32	14	26	1
S. K.	7/11	96	**129**	121	102	86	93	**108**	103	84	87	3	21	19	18	-1
	7/18	100	**148**	122	128	116	95	**136**	98	99	108	5	12	24	29	8
	7/25	98	132	**136**	114	106	100	**128**	106	97	89	-2	4	30	17	17
M. L.	7/11	88	131	**137**	101	76	85	102	**113**	96	71	3	29	24	5	5
	7/18	97	**149**	141	124	113	95	**139**	120	112	120	2	10	21	12	-7
	7/25	93	149	**153**	133	117	92	**139**	135	122	98	1	10	18	11	19
C. C.	7/14	101	**186**	179	128	117	95	131	**175**	96	109	6	55	4	32	8
	7/21	110	179	**193**	141	119	99	140	**186**	93	93	11	39	7	48	26
	7/28	88	141	**207**	127	140	90	130	**208**	115	122	-2	11	-1	12	18
S. S.	7/14	96	140	**187**	118	70	104	139	**175**	85	67	-8	1	12	33	3
	7/21	102	159	**213**	132	117	102	151	**163**	124	89	0	8	50	8	28
	7/28	98	158	**209**	154	101	97	151	**190**	125	89	1	7	19	29	12
G. C.	7/14	86	186	**209**	153	97	83	159	**171**	114	78	3	27	38	39	19
	7/21	94	182	**194**	124	122	88	168	**175**	130	121	6	14	19	-6	1
	7/28	91	191	**207**	122	102	90	173	**179**	117	82	1	18	28	5	20
J. C.	7/14	94	125	**161**	136	94	96	129	**144**	122	82	2	-4	17	14	12
	7/21	105	172	**202**	157	130	103	157	**169**	155	134	2	15	33	2	-4
	7/28	102	161	**207**	175	154	106	177	**201**	165	155	-4	-16	6	10	-1

TABLE I—CONT'D

	DATE, 1936	CUTANEOUS BLOOD F.*	0.5 HR.	1 HR.	2 HR.	3 HR.	VENOUS BLOOD F.*	0.5 HR.	1 HR.	2 HR.	3 HR.	CUT.-VEN. DIFFERENCE F.*	0.5 HR.	1 HR.	2 HR.	3 HR.
E. W.	7/14	86	142	**153**	145	99	88	128	**142**	140	86	-2	14	11	5	13
	7/21	92	152	**162**	150	124	95	149	**158**	142	127	-3	3	4	8	-3
	7/28	92	157	**185**	131	125	96	147	**169**	123	115	-4	10	16	8	10
A. C.	7/15	89	**137**	111	101	104	85	**114**	92	84	98	4	23	19	17	6
	7/22	85	**112**	108	115	104	86	**101**	87	71	79	-1	11	21	44	25
	7/29	92	**156**	137	135	115	92	**139**	120	112	111	0	17	17	23	4
L. T.	7/16	92	147	**154**	141	130	95	130	**135**	121	110	-3	3	19	20	20
	7/23	109	**182**	154	126	108	102	**148**	130	101	97	7	34	24	25	11
	7/30	88	**135**	134	123	114	83	**124**	118	97	106	5	11	16	26	8
J. G.	7/25	95	159	**181**	142	134	93	138	**148**	115	114	2	21	33	27	20
	8/ 1	90	**155**	151	124	129	88	**130**	126	100	116	2	25	25	24	13
	8/ 8	106	147	**149**	144	142	102	129	**131**	124	128	4	18	18	20	14
J. S.	7/25	87	**146**	119	90	97	89	**129**	99	81	91	-2	17	20	9	6
	8/ 1	89	**151**	113	118	117	88	**115**	97	89	103	1	36	16	29	14
	8/ 8	91	**173**	121	100	100	83	**131**	93	76	90	8	42	28	24	10
L. U.	7/27	101	**199**	197	141	86	95	**186**	199	131	82	6	13	-2	10	4
	8/ 3	88	**174**	165	119	75	84	**157**	143	109	73	4	17	22	10	2
	8/10	90	178	**252**	203	112	84	177	**227**	198	109	6	1	25	5	3
N. T.	7/27	106	152	**196**	133	122	102	152	**205**	114	119	4	0	-9	19	3
	8/ 3	100	174	**212**	135	116	97	152	**164**	111	102	3	22	48	24	14
	8/10	103	151	**213**	154	81	97	151	**191**	117	78	6	0	22	37	3
L. N.	7/29	86	134	**187**	125	77	84	129	**169**	103	77	2	5	16	22	0
	8/ 5	94	137	**166**	142	136	89	135	**150**	122	76	5	2	16	20	60
	8/12	85	137	**191**	168	125	83	137	**160**	140	108	2	0	31	28	17
A. H.	7/30	88	**129**	115	102	87	99	**124**	101	83	85	-11	5	14	19	2
	8/ 6	83	**153**	132	116	90	86	**136**	100	91	79	- 3	17	32	25	11
	8/13	87	121	**136**	114	125	83	119	**126**	108	110	4	2	10	6	15
Average first test		92.5	151.1	158.5	123.2	97.2	92.0	132.7	144.2	107.2	88.3	0.5	18.4	14.3	16.0	8.9
Average second test		96.0	159.1	164.2	132.9	114.9	93.2	138.6	139.3	111.7	101.3	2.8	20.5	24.9	21.2	13.6
Average third test		93.6	152.4	170.8	137.1	115.0	92.0	152.5	170.8	119.6	103.4	1.6	11.1	19.2	17.5	11.6
Average all readings		94.0	154.0	164.5	131.0	109.0	92.2	137.5	145.0	113.0	97.5	1.8	16.5	19.5	18.0	11.5

*Fasting.

†Figures represent milligrams per cent.

there is a tendency for the blood sugar to require a greater time to return to the fasting levels.

A review of the figures of the individual analyses shows that in six instances, the first curve is higher than the second; and in four cases, it is higher than the third; while in five instances, it is of the same magnitude as the second and third curves. However, these differences are not great. In only three cases out of the 120 curves are the variations in values large enough to indicate a definite shift in the time required to reach the peak. F. M. gives a shift of peak in the second cutaneous test, and L. U. has a shift of the peak in both the cutaneous and venous values in the third test. In both the capillary and venous curves the peaks are reached within the first half hour in 9 cases, and

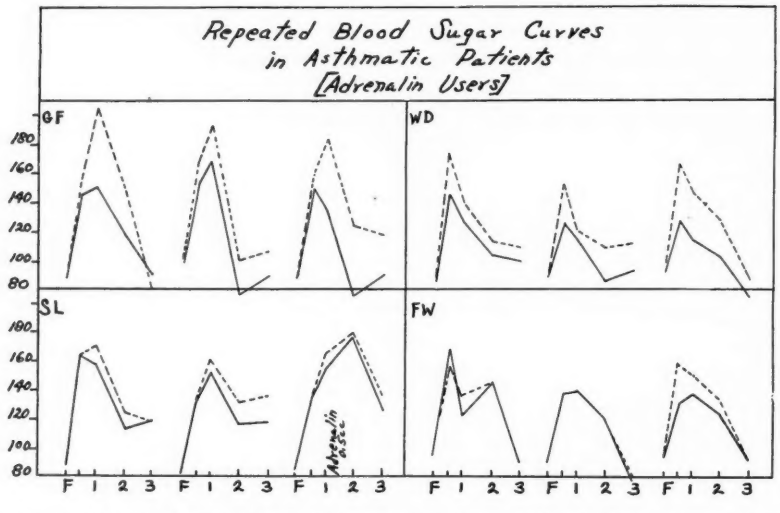

Fig. 2.—Individual sugar tolerance curves in four patients with severe asthma. (Adrenalin users.)

within the first hour in the other 11 cases. The capillary and venous peaks occur at the same time with only a single exception.

"*Adrenalin Users*" might have a different sugar tolerance. Four of our patients had asthma which was severe enough to require frequent doses of epinephrine. Three were men, one was a woman. In studying them, exactly the same procedure and method was used. The patients were instructed to avoid, if possible, the use of adrenalin in the twelve hours prior to the test, but in some instances this was impossible. The exact times of the last dose of adrenalin before the various tests are given in the protocols. Fig. 2 shows the results of the study in each of the four patients. It will be necessary to discuss them separately.

George F. was a thin, worn man of fifty-seven years whose asthma had begun at the age of fifty-one years, and who had used adrenalin every day for three years. In the twenty-four hours before the first test he had taken, subcutaneously, 7 doses

of adrenalin, each of 5 minims. On July 8, 1936, the day of the first test, he took adrenalin 5 minims at 2 A.M. and again at 5 A.M. The fasting blood samples were drawn four hours later at 9 A.M. During the test period there was no asthma. During the following week, his asthma was much improved so that his adrenalin requirement fell from 7 to 8 doses to 4 doses in each twenty-four-hour period. The second test was made at 9 A.M. on July 15 when he had had no adrenalin since 9 P.M. on the evening before. On arrival in the clinic, he was comfortable, but during the second hour, severe asthma developed, requiring adrenalin at the end of the test. During the second week, he was comfortable, and again the test was made long after the last adrenalin (this time thirteen hours). This time no attack developed during the test.

His tolerance curves are all high, the capillary curve much higher than the venous, as was observed in the other milder cases. The attack of asthma which occurred during the second test is interesting. The venous curve rose to a higher level on that day, but the fact is hard to correlate with his asthma. The terminal rise in the venous curve is interesting. Adrenalin was given after and not before this rise. The inability of the recently ingested glucose to control his asthma is evidence that the improvement of the preceding week did not depend upon any effect of the first tolerance test.

William D., aged forty-seven years, and of average build, had had mild asthma since the age of thirty-seven years, but had used adrenalin only for about two years, his average requirement at the time of study being from 3 to 4 doses a day. Each of the 3 tests was made three hours after a dose of adrenalin, and in each test an attack of asthma occurred during the last hour which required that adrenalin be given before the study was completed. On account of these circumstances, his sugar tolerance curves are particularly interesting.

The three sugar curves are essentially the same, as they do not show any significant variation from a normal nondiabetic sugar curve. There is nothing about them to indicate an effect either of the previous extensive adrenalin medication or of the existence of asthma at the time of the test. They suggest strongly that the lowering of the blood sugar, which might occur during an attack of asthma under ordinary circumstances, is in the nature of a secondary change. Here we have frank asthma with elevated blood sugar.

Sarah L., aged forty-six years, a stout Jewess, had used adrenalin 6 to 8 times a day for six years. Her asthma of the intrinsic type had begun at the age of thirty-four years. Each test was made only three hours after a dose of adrenalin, and in spite of this, asthma developed each time before the test was completed. In the third test this asthma was so severe that it was necessary to administer adrenalin directly following the taking of the one-hour blood samples. The curves of the third test are especially interesting. Even though the blood sugar continued to rise to peak values, the asthmatic symptoms became progressively worse.

Here is a good example of a case in which glucose per se had no immediate beneficial effect in relieving an attack of asthma. In spite of these facts, this individual experienced marked relief for several days

following the first and second tests. Could this indicate that beneficial effects of glucose might be delayed? The transitory effect of adrenalin is well illustrated in this instance. Six large doses of adrenalin in twenty-four hours, with the last one taken about three hours before the start of the test, did not cause an appreciable change in the sugar tolerance curve, while one dose of adrenalin given in this instance when the blood sugar levels were at previous peak values caused an immediate additional transitory rise.

Fred W., a short, thick-set man of fifty-two years, had had asthma since age of forty-seven years. While his asthma had been severe at times, there also had been long free periods without asthma. For six weeks, however, adrenalin had been necessary in 2 doses a day. At the time of study, in July, 1936, his asthma had been distinctly worse so that the number of adrenalin doses had increased. The first test was begun only five hours after the last adrenalin. During the next week, his asthma continued in severe form. The second test was made at 9 A.M. after a bad night. He had taken adrenalin at 7 P.M., 11 P.M., 4:30 A.M. and at 7 A.M., each dose being 0.50 c.c. After this second test, however, he did well for three days without any adrenalin at all, but then the bad attacks recurred as before. Before the third test, he had taken adrenalin at 6 P.M., 11 P.M., and 3 A.M. During this third test, he had asthma in the last hour, requiring adrenalin at the end. It is noted that after the third test, his symptoms were unchanged and required adrenalin 2 to 4 times a day for their control.

The sugar curves of Fred W. are quite different from those of the other adrenalin users. In the first test, there is a secondary rise similar to that described by Gilbert and others[10] in their blood sugar studies. The cutaneous and venous blood sugar levels are approximately the same in the first two curves. The third test curves are of a normal type with the typical positive cutaneous-venous difference. We cannot explain the marked variations in the three curves. They represent the single exception in our repeated tolerance studies of 25 subjects. Fred W., contrary to instructions, did not repeat the same diet the day preceding each test, but we rather doubt that this fact could explain the great variation in the three sets of curves. Sweeney[11] found marked differences in the sugar tolerance curves when his subjects were on high protein, high fat, or high carbohydrate diets, but in a second paper, he showed that the sugar tolerance curves were about the same whether his student subjects ate a standardized or a general diet.

In view of the findings in the other patients who used greater amounts of adrenalin a day, it would not seem reasonable to attribute the variations to previous adrenalin medication. On the other hand, Fred W.'s asthma, in contrast to the other cases, was of very short duration. For many months prior to six weeks before the initial sugar tolerance test, he had been free of asthma and his current attack followed a severe upper respiratory infection of two weeks' duration. It is likely that this recent infection has influenced the results obtained from the subsequent

tolerance test. This man also had asthmatic symptoms during the latter part of the third test, but the curves themselves give no evidence of its occurrence.

DISCUSSION

The observations indicate that previous frequent large doses of adrenalin, even though continued to within three hours of the ingestion of glucose in a sugar tolerance test, do not affect the size or shape of the resulting sugar curves.

The glycogen stores in the liver can be depleted by adrenalin. The fact that the sugar curves in our patients are normal may represent an actual increase in tolerance which is concerned in some way with allergy or asthma. Theoretically, such a possibility could be controlled by repeating the test on nonallergic and nonasthmatic persons, but the difficulties are great. Adrenalin is not harmless for normal men. It causes palpitation, headaches, and sweating. It raises blood pressure. To inject adrenalin in healthy normal individuals would inflict unnecessary hardship, and to give repeated doses to individuals in bed would furnish poor controls for our patients who are ambulatory. The authors must "rest their case."

The presence of asthma during 12 of the tests and in all 4 subjects did not materially influence the general shape of the curves which are similar in all respects to those obtained from other normal nondiabetic subjects. Incidentally, it was observed that high blood sugar levels and asthmatic symptoms could exist at the same time and be apparently independent of each other.

Some of the patients stated that for several days following the tolerance tests, varying amounts of relief from their asthma were experienced. Subsequently, these patients were treated with small (four teaspoonfuls) of glucose given by mouth at frequently (two hourly) intervals. At the end of a week, however, there had been no noticeable change in the asthma. The number of doses of adrenalin used in twenty-four hours remained about the same. If it is true that sugar by mouth will relieve asthma, it is evident that this sugar must be given in large doses.

SUMMARY

1. Repeated determinations of the glucose tolerance in a group of patients suffering from asthma and hay fever gave results which were essentially uniform and essentially normal. In each case the values for both the venous and capillary bloods were compared.

2. The fasting blood sugar values found in allergic individuals, even when suffering from severe asthma, falls within the range of the values found in normal nondiabetic individuals.

3. The blood sugar curves of four patients with asthma severe enough to require frequent doses of adrenalin, were plotted and found to fall within the range of the curves of other symptom-free allergic individuals.

Even though some of these patients were suffering an attack of asthma at the time of the test, or had taken adrenalin a few hours before the test, it was not possible to demonstrate any change in the sugar tolerance curve which might have revealed either the asthma or the recent dose of adrenalin.

4. We conclude that the value for blood sugar and the test for glucose tolerance in allergic patients are both normal, and as a corollary, that whatever may be the fundamental nature of allergy, it is not concerned with the blood sugar level.

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THE RÔLE OF CLADOSPORIUM, A COMMON MOLD, IN ALLERGY*

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OUR active interest in molds as allergic excitants dates back to 1923. In our earlier studies, the tests for possible sensitization to molds were performed with relatively few antigens. The number of the latter was gradually increased and the selection of new mold preparations was suggested by an enlarged experience. During the past ten years, all our private patients, other than those with seasonal hay fever, have been tested routinely with the products derived from a large variety of molds, 25 to 30 in number. The results of some of our studies have been published.[1, 2] It is our purpose to report at this time the rôle of *Cladosporium,* a common vegetable mold, in allergic conditions.

The name *Cladosporium* is applied to a great series of parasitic and saprophytic molds found upon diseased or dead vegetable material. As encountered in the field, the vegetative hyphae are mostly brown or greenish brown, rather thick-walled, either superficial or penetrating the plant tissues. Threads or hyphae penetrating masses of plant tissue tend to have thinner walls and less discoloration. Hyphae exposed directly to air and sunlight are brown-walled. The sporestalks or conidiophores and conidia are brown-walled and, as met with in the field, all or part of the conidia or spores are two-celled when ripe. Conidiophores are found as short, brown-walled branches perpendicular to the surface of the plant material and bearing at or near the apex one to many branched chains of spores.

One to several spores bud out directly from the apical cell of the conidiophore, and secondary spores from the distal ends of the primary spores as in the budding of yeasts. The spore masses resulting may include many complexly branching chains totalling hundreds of spores, with the primary spores remaining at the center, and newly formed spores at the tip of every branch. The older spores in such masses become two-celled and sometimes all of the cells become two-celled. The whole masses commonly fall apart when wet, so that each spore is free to develop into new mycelium.

In laboratory culture media, great variations occur. The cell walls may be almost colorless at first and only slowly turn greenish brown, or the whole colonies may be brown or greenish brown from the first. The budding cells in the spore chains may remain one-celled through-

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out the ordinary period of observation. Two-celled spores develop only after such colonies have been dried for several weeks.

Some species grow well at blood heat, which is prerequisite to pathogenicity. It is not, therefore, surprising to find occasional species reported in connection with diseased conditions.

Cladosporium, Alternaria and other brown-walled molds are responsible for the dirty gray to greenish black or brown color of dead and decaying vegetation as seen in the waste place, the fence corner, the field, or the garden in fall and winter. The molds are abundant also in summer, but their color is less conspicuous than the green of growing plants hence they may be overlooked. But after the first frost in the fall, these organisms are the dominant factor in the so-called "weathered" appearance of plant remains during fall and winter.

The name *Cladosporium* goes back to the German mycologist, Link, who published it in the paper referred to as Observationes II, in 1817; then it was republished in *Species plantarum* in 1824. Later Bonorden (1853) proposed to separate species with one-celled conidia in a new genus, *Hormodendrum,* leaving in *Cladosporium* those forms producing two-celled conidia only. Both names are still used in varying senses by different authorities.* The most careful observations seem to show that two-celled conidia occur to some extent in all of the species adequately studied; hence the occurrence of septa in the conidia is not regarded as justification for separating species whose general morphology offers no other diagnostic characters.

Species of *Cladosporium* are found everywhere and should be better known to allergists. Feinberg and Little,[3] in a year's survey of the daily mold spore content of the air in Chicago, state that the *Alternaria* and *Cladosporium* have been among those most frequently found in the several hundred varieties of fungi which the authors have encountered. Air studies made by Meier and Lindbergh[4] likewise reveal the presence of the spores of *Cladosporium* at an altitude of 3,000 feet above sea level, north of 70° latitude and well above the Arctic circle.

In our preliminary tests, powdered material obtained by grinding the dried "pelts" was applied to scratch marks on the skin, and these were moistened with twentieth normal sodium hydroxide solution. Of several hundred patients thus tested by the cutaneous method, four reacted positively to the *Cladosporium* preparation. The reactions were typical, as evidenced by the formation of a wheal and pseudopodia with a surrounding zone of redness. A clinical summary of this series of patients follows:

CASE 1.—Male, aged fifty-nine years, has been subject to vernal and autumnal hay fever for fifty-two years. For thirty-five years, asthma has complicated his hay fever. During the past ten years, the asthma has become perennial.

*Hormodendrum has been adopted in recent papers of A. L. Carrion[7] for a pathogenic species.

CASE 2.—Female, aged eleven years, has had perennial hay fever all her life, more pronounced during the summer months. Her asthma is of more recent origin. It is, likewise, perennial and shows a seasonal aggravation in summer.

CASE 3.—Female, aged four years, has had severe hay fever and asthma, irrespective of season, since she was three months old.

CASE 4.—Male, aged thirty-nine years, has been susceptible to "colds," especially during the winter, for seven years. He was first seen in June, 1934, having been referred by a competent rhinologist. His chief complaint was extreme stuffiness of nose with occasional paroxysm of sneezing. Impairment of sense of smell and of taste was present. Examination revealed pale and boggy enlarged turbinates which necessitated mouth breathing. The duration of his disability was two months.

It is noteworthy that the first three patients have exhibited multiple sensitiveness to test allergens. The fourth patient, however, with vasomotor rhinitis reacted only to the *Cladosporium* material. The site of the positive skin reaction in this instance was hot to touch and the sensation of itching became pronounced. The list of substances which were used in testing was comprised of epidermal and miscellaneous proteins, representative pollens, molds, and food proteins. The possible relationship of the *Cladosporium* to the allergic state was readily suggested by the sole positive reaction in Case 4. In the other three patients with perennial hay fever and asthma, the positive reaction to *Cladosporium* was one of several positive reactions to pollens and to food proteins. Accordingly, the subcutaneous test with an extract of the mold was performed in each case to determine its etiologic significance. In a previous study of multiple reactions observed in hay fever subjects, the following deduction has been drawn: "The subcutaneous reaction to pollen protein is a more critical and specific index of mucous membrane sensitiveness than the cutaneous or intracutaneous tests."

In each of the four patients, the subcutaneous administration of 0.05 c.c. of a *Cladosporium* extract in the dilution of 1:10,000 gave rise to a diffuse swelling, varying from two to four inches in diameter at the site of injection. The indurated area was surrounded by a zone of redness and was accompanied by a sensation of heat and itching. This criterion justified the employment of the *Cladosporium* mold extract in a desensitizing course of treatments. The fluid used in preparing the extract of the mold consisted of one part of Coca's solution and two parts of glycerin. The results of treatment were regarded as highly satisfactory by three patients in the alleviation of their distressing symptoms. The treatment with the mold extract, however, seemed to exercise no influence on the severe clinical course of asthma in the youngest patient of our series, Case 3.

The subject of mold allergy is worthy of further consideration, notwithstanding the very small percentage of patients who are proved to be clinically sensitive to molds. Additions to our knowledge of

specific excitants enlarge the scope of specific therapy. They make for a more accurate classification of our cases. The recognition of *Cladosporium* as an etiologic factor in four patients is the culmination of a search of several years. Our observations find corroboration in the work of Cobe[5] with a closely related mold, *Cladosporium fulvum* Cooke. Cobe reports a case of asthma in a worker in a greenhouse where tomatoes were cultivated. He was susceptible to the mold, *Cladosporium fulvum*, which appears on the leaves of tomato plants. Marked clinical relief followed a course of specific desensitization.

More recently, E. F. Guba,[6] of Waltham, Massachusetts, writes: "Greenhouse tomato growers will be interested in knowing that tomato mildew or leaf mold may cause asthma or hay fever. Some serious cases of this affliction have come to the writer's attention—the symptoms return when the person is further exposed to plants infested with the fungus or when he packs tomatoes gathered from infested plants." Guba does not state the number of allergic cases which have come to his attention. It is worthy of emphasis that *Cladosporium fulvum* Cooke is a pathogenic mold which characteristically attacks the tomato vine. The *Cladosporium* which we have had under investigation is a very common saprophyte.

SUMMARY

The mold *Cladosporium*, a common saprophyte, has been determined to be a factor in the production of the allergic state in man.

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DISCUSSION

DR. MARION B. SULZBERGER, New York.—I think we all now realize, just as Dr. Bernton and Dr. Thom have brought out, as has also been shown by other careful workers, such as Feinberg, Hopkins, and Kesten, that molds and other common fungi can sensitize in the same fashion as do ordinary pollen allergens and epidermal allergens. It must today be granted that the products caused by both pathogenic allergens and saprophytic fungi can produce the same pathologic allergic manifestations as are caused by other allergens, and that these manifestations will probably be susceptible to the same type of management as the allergic reactions produced by other commoner agents.

The only question which remains undecided is: What is the numerical significance of such manifestations based on sensitizations to fungi? What proportion of cases of asthma and of vasomotor rhinitis is actually due to molds, to monilias, to epidermophytons, to trichophytons, or to other fungi? This question only the future can decide.

I am sorry Dr. Bernton did not mention the matter of passive transference of this hypersensitivity to a mold. I should like to ask whether he has attempted this. When demonstrated, this type of reagin is extremely interesting, for it is rare, indeed, to find a passive transference antibody to the product of a living microorganism. Some years ago I was able to demonstrate and to study such antibodies to trichophytin; and this was confirmed by Dr. Tomlinson, from Dr. Tuft's Clinic.* These antibodies are specific, and they may thus be useful in the biologic classification of various fungi, by demonstrating certain possible antigenic relationships as shown in some of my investigations a few years ago.†

It may be of interest here to recall that we almost all, at some time or another, harbor trichophytons, monilias and other fungi, not only on our mucous membranes but also in our skin folds, nails, etc.; and that these organisms and their products are likely to enter the blood stream, and may thus produce manifestations such as asthma, vasomotor rhinitis and conjunctivitis by the hematogenous route. I should like to mention that I have recently observed not only the above manifestations, but also cases of chronic urticaria, of multiforme erythema, and of cellulitis and lymphangitis, all definitely proved to be due to the products of trichophyton fungi emanating from a distant and sometimes insignificant focus in the skin or nails.

Dr. Francis M. Rackemann, Boston.—Dr. Bernton quoted from Guba, who is a friend of mine. Dr. Guba is extremely sensitive to the *Cladosporium fulvum* which grows on the leaves of tomato plants. He is a horticulturalist and his job is to go around and help the commercial growers of tomato plants to rid their greenhouses of this pest. His sensitiveness interferes with his work.

He obtained for me a sample of the mold from which a culture was grown by the Department of Botany at Harvard; from the culture, an extract was made. Extracting fluid was added to the whole culture tube which was then shaken up and the fluid then passed through paper and through a Seitz filter. Dr. Guba has been receiving injections of the filtrate, as a result of which he is entirely relieved.

Dr. Guba has told me that he knows of two other men, both in the tomato industry, with the same severe symptoms due to contact with diseased tomato plants.

Dr. Philipp Schonwald, Seattle.—The importance of molds as a sensitizing agent probably varies with the climate. I am from the Pacific Northwest, famous for its humid climate, and we probably have more molds in the atmosphere than the rest of the country.

In Seattle my attention was first called to molds when I saw a patient, who is an official in a produce company. He had his first attack of asthma when his office was in an old building in Chicago, used as a storehouse for vegetables for twenty years. It was torn down.

*J. Allergy 6: 573, 1934.

†J. Immunol 23: 73, 1932.

The atmosphere smelled moldy. That was twelve years ago, and he has had asthma ever since. Coming to the Northwest his attacks of asthma became very severe.

For less than a year we have investigated the question, and I believe it is very simple to ascertain whether there are many molds in the atmosphere and whether they are pathogenic.

A Petri dish, containing the proper medium, when exposed to the atmosphere for a half hour, will give abundant growth of molds.

In Seattle the most prominent molds in the atmosphere belong to the *Aspergillus* and *Penicillium* type; in this one particular patient we have had about 90 per cent relief with proper mold extract treatment.

It is hard to get much information about molds. The question seems to be barely touched. I believe it is worth while to look into this subject.

Interesting to me was a remark in the *National Geographic Magazine* of May, relating the experiences of the highest stratosphere flight. They found molds, I believe *Cladosporium,* at a height of 72,000 feet.

As far as the treatment is concerned, we have not had much to go by and we had to pioneer. So far I have not dared to give subcutaneous administration of mold extracts. We use a dilution of one to one million intracutaneously every day or every other day and gradually increase it to one to one thousand.

Dr. Robert W. Lamson, Los Angeles.—Are we certain that this is a clinical allergic mechanism, or may it not be possible for anyone to develop mold sensitivity? The development of a tubercle, after introduction of living or dead tubercle bacilli, results in a skin sensitivity to tuberculin. This is a type of allergy, but not the one with which we are most concerned. Block, many years ago, showed that anyone could be sensitized to primrose, but this was not quite identical with clinical allergy. Several years ago, Towey and others* reported that 33 per cent of their patients exposed to a mold in maple bark developed a skin sensitivity to the fungus and many of the individuals developed so-called asthma. The supposed allergic nature of these reactions has not been accepted by all. I believe Dr. Huber knows something about these cases which may bear on my question.

Dr. Samuel M. Feinberg, Chicago.—The problem of mold allergy is very much like the problem of pollen allergy. Quantitatively and qualitatively, I think there could not be any agreement among any of us as to what the general problem of pollen allergy is. It would not apply to every part of the country. I believe that is true, most likely, of molds, both of allergy and findings in the atmosphere.

Around the Chicago area, we have a lot of molds, a lot of mold spores in the air, and we have certain types. A plate I am passing around is quite representative of this at this time of the year. Half of the number of colonies are of *Hormodendrum* (or *Cladosporium*). I think both of these probably are primarily the same.

In our section of the country I have found clinically that *Alternaria* are the most important, and I mean clinically; I do not mean merely by skin test, but actually by observation, day by day, in relation to the plate counts and in relation to the patient's symptoms, and in a good number of cases in relation to the results of specific therapy.

*J. A. M. A. 99: 453, 1932.

I have treated 28 patients out of a series of 54, with the indicated mold extract, and the results were just as satisfactory as, or perhaps a bit more so than, the usual specific pollen treatment.

I wish I could show one slide to illustrate my point as to the frequency of reaction, in a series of patients whose symptoms are more or less seasonal, although on closer inquiry many had some symptoms in the winter. Out of 54 patients, 52 reacted on skin test to *Alternaria*, scratch test with ordinary dried material, and 9 reacted to *Hormodendrum* or *Cladosporium*. You can see we have some other molds, but they are not included in this particular table.

Most of my treatment has been with *Alternaria*, because I have seen more indication of clinical correlation between the air content and the symptoms. We have now been making daily exposures of plates for nearly two years, and I believe we know a little about what is going on in the air in relation to molds and allergy, at least in Chicago.

DR. ROWE.—I want to know if those are just routine cases of hay fever.

DR. FEINBERG.—No. These are a group of selected patients whose symptoms I could definitely establish were due primarily to fungi. This was determined by observation, skin test, passive transfers, or some other means, and in 28 of these it was proved still further by therapy.

DR. HARRY L. HUBER, Chicago.—I want to make one correction of a statement Dr. Lamson made about the study of maple spore bronchitis in Michigan. We found that about 25 per cent of those working in railroad tie plants had a respiratory disorder caused by inhalation of spores. We did not find them skin sensitive by the scratch or intradermal method.

DR. LAMSON.—Other workers did, did they not?

DR. HUBER.—We saw a number of them, but the number of those who were affected by this was so great that it did not seem it could be allergy. These patients cleared up very promptly when hospitalized, and had the symptoms recur after being back at work a short time. It seemed to me that the inhalation of spores caused a mechanical irritation.

Last year I reported a study of the sputum of fifteen chronic asthmatics, six of which gave us cultures of *Monilia*, and of these six cultures, only two proved by inoculation into rabbits to be pathogenic. There are many of this group of organisms that we inhale that do not seem to be pathogenic.

DR. ERNEST L. MACQUIDDY, Omaha.—I think we all owe a debt of gratitude to Dr. Bernton for starting most of us in this type of work. The main difficulty is that the mycologists who know spores live in a world apart from medical men. Dr. Bernton has the unique advantage over the rest of us, in working with Dr. Thom.

Thanks to the St. Louis Botanical Gardens, I have a full-time mycologist working with me, so we are able to study the effects of the molds in allergic conditions.

I think we are overlooking a bet when we try to assume that most allergic fungus conditions are similar to hay fever and due to inhalation. Consider the type of infection that the mold and the spore would give us, such as the dermatologists have shown us for a number of years. It is a very low grade, chronic type of infection, and I do not know how

you would expect to find it by any other means than by culture. Certainly from the x-ray standpoint, you could not expect to find it, unless far advanced, and I do feel that in some of these cases we are dealing with local infections within the body. I feel that it is possible to have a fungus infection similar to what we have been talking about with bacterial allergy.

Our work is yet too new to make any statements whatever about it. There is just one thought I should like to leave with you. Potassium iodide has been used for everything under the sun and we still use it as our stock in trade in asthma. I have been using large doses of potassium iodide orally, and sodium iodide intravenously, and I think my results with these drugs, in cases where we think we have a fungus as the cause of asthma, are almost as good as, if not better than, the injections of the vaccine made up from the spore itself.

Dr. M. Murray Peshkin, New York.—Dr. Bernton interested me in the use of molds in 1932. Since then over 1,200 patients have been tested and carefully studied by me for mold sensitivity. My main problem is to study the incidence and significance of mold sensitivity in allergic cases. At the present time no definite statement can be given with regard to the rôle of mold sensitivity. However, it can be stated that in an appreciable number of patients with positive reactions on direct test passive transfer tests showed a high percentage of positive reactions.

Dr. Warren T. Vaughan.—Down in "ole Virginny" there are a lot of old houses. This is true of all of the southeastern states. There are some of them that are so old that they have become almost museum pieces, and it is a mark of distinction to be able to live in them, so that there are a lot of people living in old houses and exposed to molds, chiefly because in the early settlements the houses were all built up along the rivers, and their cellars are plenty moldy.

We put out mold plates in the homes practically routinely and never fail to find plenty of molds. We then make cultures of these mold plates, test the patients with the individual molds from their own homes, identify the molds and proceed with hypodermic medication when the patient is found sensitive. Moving from the old, moldy house into a new house does not solve the problem because the molds are carried on the furniture and promptly distributed through the new house.

Now the striking thing is the frequency of sensitization to mold, and to the yeasts and the yeastlike fungi such as *Monilia*. We realize that many such reactions are probably not specific, but we do see a surprising number of prompt reactions with pseudopod formation and a much larger number of delayed positives. We have no hesitancy in treating either type of reaction, and we could not get along without the monilia allergens in treatment.

Fortunately for those who are not in a position to make their own autogenous mold plates, we find that usually the *Monilia albicans* extract, put out under the trade name "Oidiomycin," reacts very well and can be used for routine testing. We see vasomotor rhinitis and asthma, not in large numbers, to be sure, but definitely due to molds.

Dr. Harry S. Bernton (closing).—I am of the opinion that every allergist should have a supply of mold allergens for routine testing. He will thus be enabled to help a few individuals who otherwise would be "missed cases."

Special Reports

REPORT OF COMMITTEE ON INSTRUCTION*

ASSOCIATION FOR THE STUDY OF ALLERGY

OSCAR SWINEFORD, JR., M.D., CHAIRMAN, UNIVERSITY, VA.

AT THE meeting of the Association for the Study of Allergy in Cleveland in June, 1934, the question was raised as to whether instruction in the allergic diseases occupied as important a place in the curriculums of our medical schools as an estimated incidence of active allergic manifestations in 7 per cent to 10 per cent of our population would justify.

The committee appointed to study this problem prepared the following questionnaire which was sent to the deans of all the recognized medical schools of the United States.

It was necessary to send the questionnaire to some of the schools six times before obtaining a reply. All finally replied. Only 13 answered the questionnaire fully. There were too few answers to questions 3b, 4, 5b, 6, 7d and f, and 9 to justify comment. In general the replies to the other nonstatistical questions were satisfactory. As was to be expected, a number were somewhat vague. All in all, the report gives, we believe, a good general idea of the status of instruction in the allergic diseases, although some inaccuracies are undoubtedly present.

The replies to questions 1a, 5a, 7a, b, c, e and g, and 8 are grouped for convenience in Table I.

ALLERGY QUESTIONNAIRE

1. Is there a separate allergy department or clinic?
   How long has it been operating?
   How many members of your teaching staff have their chief interest in allergy?

	NEW	RETURN	TOTAL
Internal medicine			
Pediatrics			
Dermatology			
Neurology			
Allergy			
All others			

*Read before the Twelfth Annual Meeting of the Association for the Study of Allergy, Kansas City, Mo., May 11, 1936.

2. How many cases of all sorts are studied each year by these teaching services?
3. In the table below please insert:
   (a) The number of hours of didactic instruction by the departments which teach and treat the diseases listed.
   (b) The number of cases of these diseases studied in your teaching services last year.

DISEASE	(A) DEPARTMENT					
	ALLERGY	INTERNAL MEDICINE	PEDIATRICS	DERMATOLOGY	NEUROLOGY	OTHER SERVICES
Hay fever						
Asthma						
Urticaria						
Angioneurotic edema						
Eczema						
Migraine						
Mucous colitis						
Serum reactions						

DISEASE	(B) NO. CASES		
	NEW	RETURN	TOTAL
Hay fever			
Asthma			
Urticaria			
Angioneurotic edema			
Eczema			
Migraine			
Mucous colitis			
Serum reactions			

4. Total number of hours each student receives clinical instruction (didactic, dispensary, wards, clinics) in:
   (a) The nonsurgical diseases?
   (b) The allergic diseases?
5. Has the time allotted to instruction in the allergic diseases been increased in the last five years? By what percentage?
6. Of the total number of cases assigned to each student approximately what percentage is:
   (a) Surgical?
   (b) Nonsurgical?
   (c) Allergic?
7. Are students required to or shown how to:
   Make pollen extracts?
   Make dust extracts?
   Administer extracts?
   Treat reactions to injections of extracts?

Perform skin tests:
Scratch?
Intradermal?
Passive transfer?
Perform frigothermal tests?
Take detailed food, inhalant, contact, focal infection, drug, and physical allergy histories?

8. Is there an elective course for more detailed study of the allergic diseases?
9. Please outline any plans or ideas you have for improving instruction in allergic diseases.

Signature _____, Dean
_____ Medical School.

REPLIES TO QUESTIONNAIRE

TABLE I

Summary of Replies to Questions 1a, 5a, 7a, b, c, e, g, and 8

QUESTION		NUMBER OF REPLIES TO QUESTION	YES	NO
1a	Is there an allergy clinic?	57	43*	14
5a	Has instruction been increased in past five years?	52	28	24
7	Are students taught to:			
a	Make pollen extracts?	52	11	41
b	Make dust extracts?	53	12	41
c	Administer extracts?	53	31	22
e	Do skin tests?	54	38	16
g	Take detailed allergy histories?	54	37	17
8	Is there an elective course for more detailed study?	55	17	38

*7 of these are not used at all for teaching.
4 are used only in elective courses.

It will be seen from Table I that (Reply 1a) in fourteen of 57 schools which answered, there is no allergy clinic or department and seven of the 43 clinics are not used at all for teaching and four are used only for elective courses.

(Reply 5a.) Twenty-eight of 52 schools have increased instruction in these diseases in the past five years.

(Replies 7a, b, and c.) Only about one-fifth of the schools teach the students how to make pollen or dust extracts, and in more than one-third they are not taught how to administer extracts.

(Reply 7e.) In 16 of 54 schools they are not taught how to do routine testing.

(Reply 7g.) In 17 they are not taught how to take allergic histories.

(Reply 8.) Only seventeen schools offer elective courses to those who wish to learn more about the subject.

Only 13 schools answered question 2 in sufficient detail to permit analysis. The replies are summarized in Table II.

Although so few schools were able to answer this question, the totals of 120,206 new cases and 951,784 total visits are of sufficient magnitude to be of interest. New allergy cases represent 2.2 per cent of the total number of new cases and over 5 per cent of the number of new medical, pediatric and dermatologic cases. Total allergy visits represent 4 per cent of all visits and over 9 per cent of all medical, pediatric, and dermatologic visits.

TABLE II

Summary of Replies to Question 2

	NEW CASES	TOTAL VISITS
Internal medicine	29,120	227,093
Pediatrics	9,822	97,803
Dermatology	9,321	80,811
Neurology	3,666	26,290
Allergy	2,605	37,360
All others	65,672	482,427
Total	120,206	951,784

Inasmuch as these cases represent, in the main, allergic manifestations which are sufficiently typical and severe to direct them to the allergy clinics, it is quite probable that the estimated incidence of 7 to 10 per cent is correct for the country as a whole.

Replies to questions 1b, 1c, and 3a are analyzed in Table III.

(Reply 1b.) Seven new clinics (37 replies) were established in the last two years, 13 others in the previous three years. Six are less than and 11 are more than ten years old.

(Reply 1c.) In 19 schools (54 replies) there is one and in 15 there are two instructors who have their chief interest in allergy. In three there are no instructors who are especially interested in allergy.

(Reply 3a.) In seven schools (63 replies) there seemed to be no planned instruction in allergy whatever. In 22 the instruction is limited to clinical discussions (case teaching) and short assignments in the allergy clinic. In 13 others the didactic instruction is five hours or less. In only 13 schools is the didactic instruction as much as ten hours.

DISCUSSION

In general the questionnaire shows that there is an increasing interest in instruction in allergy. But in particular it is felt that those schools which have no planned instruction whatever, which do not have allergy clinics or do not use them for teaching, which do not instruct their students at least in the theoretical and practical aspects of the administration of specific extracts, routine skin testing, and allergy history taking, are grossly unjust to their students and to 5 to 10 per cent of the patients they will be called upon to treat.

TABLE III

Summary of Replies to Questions 1b, 1c, and 3a

QUESTION		NUMBER OF REPLIES TO QUESTION							
1b	How long has clinic been operating?	37	Number of years	1-2		3-5		6-9	Over 10
			Number of clinics	7		13		6	11
1c	Number of teachers whose chief interest is allergy?	54	Number of teachers	1	2	3	4	5	6	0
			Number of schools	19	15	11	4	1	1	3
3a	Number of hours of didactic teaching?	63	Number of hours	0	2-5	6-9	Over 10	Clinical Only		
			Number of schools	7	13	8	13	22		

There are several points, most of which were discussed in some detail by Balyeat[1] six years ago, which the committee would like to emphasize: (1) that the vast majority of the physicians of this country have an appalling lack of knowledge concerning allergic diseases; (2) that entirely too many physicians fail to recognize allergic manifestations unless they are perfectly typical, and even typical manifestations commonly go unrecognized; (3) that most of the information many physicians have is obtained from literature put out by commercial firms, which obviously attempts to simplify the problems of diagnosis and treatment to a degree entirely inconsistent with the needs of perhaps one-half the cases seen in the average practice; such simplification by its inadequacy tends to create an undeservedly pessimistic impression of the prognosis in this group of diseases; (4) that the assignment of the teaching of allergic diseases to members of the departments of medicine, pediatrics, and dermatology who do not have a deep interest in allergy is undesirable; unless the instructor is deeply interested he is likely to overemphasize the recognition of the clinical manifestations (which are usually absurdly easy to recognize) at the expense of the problems of therapy and of etiologic diagnosis which are complex and important to a degree not equalled in any other branch of medicine.

The committee makes the following recommendations:

1. That the committee on curriculums of the Association of American Medical Colleges be urged to require: (a) the inclusion of planned instruction in the allergic diseases in the curriculums of all recognized medical schools; (b) that the minimum acceptable instruction include discussions of the pathology, pathologic physiology, clinical manifestations, diagnostic methods including skin testing and elimination procedures, the preparation of diagnostic and therapeutic extracts, the essentials of history taking, the principles of specific, symptomatic, and nonspecific therapy, and the practical clinical application of these principles; (c) that instruction in these diseases be assigned to teachers whose chief interest is in the field of allergy; (d) that instruction in these diseases be accorded the relative place in the curriculums which their incidence and severity would seem to justify.

2. That this report be submitted to the officers of the Society for approval of all its details and implications before being sent to: (a) the deans of all medical schools; (b) the committee on curriculums of the American Association of Medical Colleges; (c) the editor of the JOURNAL OF ALLERGY with a request to publish it; (d) the editor of the J. A. M. A. with a request to give it editorial recognition.

Assuming that expense has been the chief obstacle to the inclusion of adequate instruction in allergy in the curriculums of certain schools, a plan of instruction is offered which has been used successfully with negligible cost for the past six years.

The allergy clinic meets one afternoon a week in quarters used by one of the morning clinics. Skin tests are done by the central clinical pathology laboratory (this plan must of course be adapted to the needs of the individual institution).

Patients having allergic manifestations are put through an allergy routine by the students in the medical, dermatology, and pediatric clinics. The students report to the allergy clinic with their patients at its next meeting. The instructor then reviews the clinical, diagnostic and therapeutic features of the case with the student who reports with the patient, by appointment, to the clinic for subsequent observations as long as he is on the pediatric or medical or dermatology service.

The allergy routine consists of a detailed medical and allergy history, complete physical examination, skin test, urinalysis, hemoglobin, Wassermann on all patients, consultation with the dentist and the rhinolaryngologist when indicated; gastric analyses and frigothermal tests on those who have gastrointestinal symptoms or who think they are affected by physical influences. The students do or witness all of these procedures. The allergy history is recorded on a form which has the following headings: Chief complaint, other allergic manifestations, family history of allergy, onset of present illness, description of present illness, description of occupation and environment, effects of foods, effects of inhalants, effects of physical influences, contact and drug idiosyncracies, symptoms and signs suggesting focal infections, systemic history and physical examination, and studies indicated for the particular patient.

The same routine is carried out on allergy patients on the wards except that the instructor sees the patient by consultation in the hospital. The ward patients are also discussed on the regular medical, pediatric and dermatologic teaching rounds.

In addition to the above, there is one lecture in the first year devoted to anaphylaxis, with demonstrations of shock, stressing the relationships to immunity, on the one hand, and clinical allergy, on the other.

In the third year there are eight lectures devoted to discussions of the clinical manifestations, the pathology, the pathologic physiology, diagnostic procedures, the preparation of simple extracts, the principles of symptomatic, specific and nonspecific therapy with emphasis on pollen treatments.

With this plan all allergy patients are carefully studied; no especial equipment or personnel is required except for skin testing and instructors. In the clinic described there is only one instructor and one or two volunteer assistants from the house officer staff; there are no clerical or technical assistants. Between 10 and 20 patients are seen at each meeting of the clinic. Common pollen and other treatment extracts are supplied without cost to the patient at a total cost to the instructor of about ten dollars per year.

The committee wishes to emphasize from actual experience that a fairly efficient allergy teaching service can be operated for between 600 and 1,000 visits per year on a negligible budget by one instructor who can devote three to five hours a week to it.

REFERENCE

Balyeat, R. M.: Survey of Medical School of United States Relative to Teaching of Diseases Due to Allergy, J. A. M. A. 5: 276, 1930.

DISCUSSION

DR. NARCISSE F. THIBERGE, New Orleans.—There is one point which the report of Dr. Swineford did not bring out: the length of time in which the oldest clinic in the United States has been established.

The oldest clinic in the United States was established in Louisiana, connected with the Charity Hospital. This was in 1916 by Dr. Shepergill and myself; connected to it is the Louisiana State University, where each student receives 27 hours of instructions in allergy.

TULIP BULB DERMATITIS*

BEN Z. RAPPAPORT, M.D., AND WILLIAM H. WELKER, PH.D.
CHICAGO, ILL.

THIS work was reported in 1933 before the Chicago Allergy Society with a demonstration of the reactions to the skin test. Since then observations on tulip bulb dermatitis have been made by other workers. Bertwistle[1] in 1935 states that up to 85 per cent of the workers in Holland develop this condition. It occurs there chiefly in the period from July to October when bulbs are lifted and graded. A great number of cases occur especially when short-stalked bulbs are cut open to increase their length. This author reports the onset of symptoms in English workers twelve hours after handling the bulbs, with tingling of the finger tips under the nails. More recently Caulfeild[2] reported, without knowledge of our work since it had not been published, that the active material was ether soluble. He treated the patient successfully with the ether soluble extract taken up in corn oil. Hyacinth bulbs have also been reported as causing dermatitis of the hands.[3] An inquiry directed to one of the large seed and bulb concerns in the city of Chicago elicited the fact that it is known that certain individuals have suffered disturbances similar to those reported here during the time that they were handling bulbs, although specific knowledge as to which type of bulb was the offender was lacking. It would seem probable that such disturbances are much more common than we originally suspected.

The appearance of the finger tips of an individual who handled bulbs in one of the large department stores in the city of Chicago led to questioning.

CASE REPORT

Male, aged thirty-five years, complained of skin lesions of the hands. These were seasonal in development, with subsidence and recurrence for the preceding four years. Each August his fingers would begin to itch and swell. The condition started at the tips of the fingers, more marked in the right index and thumb. The other fingers of each hand became involved. Swelling and itching became intense from day to day, until in a few days the fingers of both hands were raw, swollen, and moist. The finger tips were almost black in color. The superficial skin over the fingers was exfoliated in irregular patches, leaving areas of superficial ulceration. The condition lasted until about mid-September and then gradually subsided. During the rest of the year his hands were perfectly normal. The patient had no other complaint of an allergic nature. His past history and his family history were also negative for allergy. During the weeks that his hands were affected, he handled regularly a large number of paper white narcissus and tulip bulbs. These were immediately suspected as the cause of his trouble.

*From the Department of Physiological Chemistry and the Department of Medicine, College of Medicine of the University of Illinois, Chicago, Ill.

A bulb of each was ground in a mortar with sand and a small amount of saline, and scratch tests were made with each of the materials. These tests were negative at the end of an hour. At the end of twenty-four hours the patient was seen again. The test site made with the tulip extract showed an area about 1 cm. across which was slightly raised, brownish, and scaly. Itching was present over this area. This subsided in several days. The narcissus test site showed no reaction. The tests were repeated with similar results. No Prausnitz-Küstner antibodies could be demonstrated in passive transfer attempts.

A study was next made to determine which constituent of the tulip bulb affected the patient. A tulip bulb extract made with 10 per cent sodium chloride was defatted with ether. The defatted solution was dialyzed against distilled water. The precipitate which appeared on dialysis was filtered off and redissolved in 10 per cent salt solution and again dialyzed. The precipitate which was formed was washed with distilled water and dried. The supernatant liquid from the first dialysis was dried and constituted the albumin fraction. The ether extract of the first 10 per cent sodium chloride solution was filtered and evaporated to dryness. The residue was extracted with absolute ether.

Patch tests were then made with the ether soluble material, the water soluble material (albumin) and with the salt soluble material (mainly globulin). The sites tested with the protein materials showed no reaction at the end of 24, 48, and 72 hours. At the site of the ether soluble material there appeared first an itching area of edema about 2 cm. across at the end of twelve hours. At the end of twenty-four hours this area was a typical eczematoid papule which was brownish and scaling. It began to subside in about a week.

The patient was instructed to protect his hands by using rubber gloves while handling tulip bulbs. He has done this, and during the last six years has had no recurrence of his lesions except when careless in the handling of the bulbs.

SUMMARY

A case of tulip bulb dermatitis of the hands is described. The toxic reacting substance was present in the ether soluble fraction of the plant and absent from the albumin and globulin fractions.

REFERENCES

1. Bertwistle, A. P.: Brit. M. J. **2**: 255, 1935.
2. Caulfeild, A. H. W.: Canad. M. A. J. **34**: 506, 1936.
3. Johnson, D. W.: Arch. Dermat. & Syph. **32**: 289, 1935.

AN UNUSUAL CASE OF SPINACH HYPERSENSITIVENESS*

BENJAMIN ZOHN, M.D.
BROOKLYN, N. Y.

CASE REPORT

H. T., a fruit and vegetable dealer, aged fifty-four years, was admitted to the . clinic on September 14, 1934, complaining of asthma and a local skin condition on his hands of one year's duration. There was no history of allergy in either of his parents or in his 2 children. His past personal history was irrelevant. The present illness began one year ago. He had been working in fruit and vegetable stores for the past three years, but symptoms of asthma first developed within the past year. They occurred whenever the patient went into his store. His mere presence there for a short while, whether in direct contact with vegetables or not, was enough to precipitate an attack of dyspnea. This usually lasted twenty-four hours and was followed by a productive cough. Handling the vegetables would often cause the skin of the hands and particularly the fingers to crack open and bleed.

Examination revealed a rather well-nourished plethoric individual, not acutely ill. There was congestion of the nasopharynx with rather enlarged cryptic tonsils. The mucous membrane of the nose was somewhat red. The breathing space in both nares was adequate. On transillumination the left frontal sinus appeared somewhat darker than right, and both maxillary sinuses were opaque. The chest was somewhat emphysematous. The lungs contained many sibilant and sonorous râles. There was enlargement of base of heart which could be detected readily by percussion. The blood pressure was 140/80.

X-ray of the sinuses disclosed a veiling of right maxillary sinus. X-ray of the chest showed a diffuse bilateral accentuation of the bronchial and vascular markings. The hilus was moderately thickened due to heavy root branches. The arcus was knuckled. The roentgenologic diagnosis was diffuse peribronchitis; hilus thickening; and aortitis.

The blood Wassermann was negative. The blood count was normal.

The skin of hands presented an interesting picture. A detailed description of it by a dermatologist was as follows: "The dorsa of both hands and fingers especially in the interdigital spaces reveal patches of erythema not sharply outlined and surmounted by furfuraceous scales but without infiltration. At the inner parts of all fingers are erythematous areas surmounted by tiny pinhead-sized vesicles. All the nails at the roots show transverse indentation, the process being limited only to the linula. This simulates fungus infection of the nails. The tips of all fingers show a little cracking with slight exfoliation. The palms of the hands and the wrists show erythematous patches with slight scaling. On the left foot between the second and the fourth interdigital spaces, there is exfoliation and maceration of epidermis. The right foot between the fourth and the fifth interdigital spaces shows the same process." Diagnosis: "Trichophyton infection of the hands with a superimposed dermatitis of allergic nature."

Skin tests were performed by the intracutaneous method employing Coca's extracts with the positive results shown in Table I.

*From Allergy Clinic of Beth Moses Hospital, Brooklyn, N. Y.

TABLE I

	MG. N. PER C.C. OR DILUTION	BY DIRECT SKIN TEST	BY PASSIVE TRANSFER TEST	BY PATCH TEST
Wool	0.1	Moderate		
Dust	1:10	Moderate		
Feathers	1.0	Moderate		
Rye	0.05	Moderate	Slight	Negative
Green peas	1:10	Marked	Slight plus	Negative
Spinach	1:10	Marked plus	*Marked plus*	Negative
Almonds	0.05	Marked	Slight	Negative
Lima beans	1:10	Slight to moderate	Negative	Negative
Tomatoes	1:5	Slight to moderate	Negative	Negative
Carrots	1:5	Slight to moderate	Negative	Negative
Asparagus	1:5	Slight	Negative	Negative
Cabbage	1:5	Moderate	Slight	Negative
Grape	1:5	Marked	Slight	Negative

Skin tests were also done with oidomycin 1 to 100 dilution. Within twenty-four hours, there was slight redness about site of injection. Within seventy-two hours the redness increased slightly and the site became somewhat indurated and bronzed. Trichophytin 1 to 30 failed to give any reaction within seventy-two hours.

The bulk of evidence pointed definitely to spinach as the greatest offender in this case and, to a lesser degree, to green peas. Emphasis was therefore placed on the study of spinach as the etiologic factor.

Patch tests with spinach were made on this patient at least five or six times on different occasions. Various technics were employed. Patch tests were done with the leaf and stalk together or separately, and with spinach that was extracted with ether. Patch tests were also performed with these materials on abraded surfaces. At no time was a positive reaction obtained.

Serum Studies.—A normal substitute was sensitized on several sites by the intracutaneous injection of the patient's serum according to the technic of Walzer.[1] These sites were prepared on the right arm on September 5, 1936. Skin tests were performed on these sites on September 10 to check the positive reactions obtained by the direct method of testing. The results of these tests are listed in Table I.

On September 12, with the same serum and the same substitute, a number of sites were prepared on the left arm. On September 19, this subject ate about two tablespoonfuls of cooked spinach. All the new sites on the left arm lit up, and in addition those sites upon which skin tests had been made the previous week.

On September 30, some new sites were prepared on the same substitute. On October 4, some fresh spinach contained in a paper bag was held close to the substitute's nose for a period of about three minutes. No reaction was obtained at the local passively transferred sites during a period of observation of one hour. Subsequently spinach powder (Arlington) was insufflated into the nostrils of same individual; but no reaction at the local sites was obtained.

The high titer of spinach antibodies in the serum was demonstrated in the following manner. Dilutions of serum were made in the strengths of

1:16, 1:64, 1:256, and 1:1,024. A substitute was injected with the serum in these dilutions. These sites were subsequently tested with spinach 1:10. The following results were obtained.

SERUM DILUTION	RESULT
1:16	Marked plus
1:64	Marked
1:256	Moderate
1:1,024	Slight plus

The potency of this serum was further demonstrated by testing the sites prepared with undiluted serum with increasing dilution of antigen. The results obtained with this procedure were as follows:

UNDILUTED SERUM	DILUTION OF ANTIGEN	REACTION
Site 1	Spinach 1:100	Marked
Site 2	Spinach 1:1,000	Marked
Site 3	Spinach 1:10,000	Moderate
Site 4	Spinach 1:100,000	Slight

Clinical Tests.—Observations were made on the patient by exposing him to various vegetables by contact, inhalation, ingestion, and injection.

When this patient handled spinach, he developed a severe itching between his fingers almost at once. The skin over this area would soon crack open. The pruritis disappeared after thorough washing of the hands. The cutaneous manifestation was always accompanied within a few hours by an attack of asthma.

When some fresh spinach was placed in a paper bag and held near the patient's nose for a few minutes, he developed an asthmatic attack within twenty minutes. This lasted for several hours. The skin of the fingers and hands was not affected by this procedure.

At another time, some spinach was prepared outside the patient's house, so that he was not exposed to the odors of the cooking of the vegetable. He was then given three tablespoonfuls of this dish. Within five minutes after its ingestion, he developed a sensation of distention in his abdomen. His eyes began to itch, and an attack of dyspnea developed which lasted for several hours. His fingers were not affected by this test although an itch of the left forearm was noticed without any apparent local signs. The asthma and itching lasted for about three hours. The following day he complained of severe cramps, but experienced no diarrhea or vomiting.

Handling of green peas did not affect the hands, but caused sneezing. Within two hours the patient developed asthma, which lasted about 8 to 10 hours. This was followed by a cough for several days.

Inhalation of green peas in a manner similar to that employed with spinach produced only occasional sneezing but no asthma.

Ingestion of green peas produced severe cramps, slight itching of eyes, but no asthma or local skin condition. This lasted for several hours.

Other vegetables including tomatoes, string beans, cabbage, lettuce, sour grass, and beet tops failed to give any reaction either by contact, ingestion, or inhalation.

Treatment.—At the onset, this patient was given stock dust and vaccine injections. These were subsequently followed by injections of dust extract made from sweepings of the vegetable store where he was employed. The results were unsatisfactory. The patient felt well at home, but on entering the vegetable store, he would experience an attack. Some forms of shock therapy were then attempted with no favorable results. Treatment with the specific antigens to which the patient was sensitive has not been encouraging. Injections of spinach extract were given commencing with 0.1 c.c. of spinach 1:100 dilution. The injection of 0.4 c.c.

of spinach 1:10 dilution induced a severe constitutional reaction in the form of asthma and a severe local reaction at the site of injection, but no eczema. Injections with increasing doses of green peas failed to produce any severe local or constitutional reactions.

COMMENT

This case is presented because of its unusual nature. Spinach frequently causes asthma by ingestion, but by inhalation it is a rare offender.

Another interesting feature of the case is the variable response of the shock organ to different methods of contact with the offending antigen. Mere contact of the skin with spinach produces only irritative local symptoms. Ingestion of this food gives gastro-intestinal symptoms and asthma, but no local visible skin manifestations on the hands. Inhalation of the antigen produces only asthma. Injection of the spinach extract in excessive amount produces only asthma.

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REFERENCE

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Annual Review

ALLERGY IN DERMATOLOGY

A Critical Review of Some Recent Contributions

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IN PRESENTING this year's review of selected contributions to dermatologic allergy, the sequence and arrangement of last year's article will be maintained as far as possible. In my first review, I felt that it was advisable to devote considerable attention to the preceding older publications. This will not be necessary in the present brief summary.

1. Eczematous Dermatitis of Allergic Origin
Contact Dermatitis

The recent contributions have, in general, served to emphasize the necessity for distinguishing with the greatest possible clarity between atopic dermatitis and eczematous dermatitis of contact type. The number of the substances which have been found to be capable of producing allergic contact dermatitis is constantly increasing. A detailed compilation will be found in the new list published by L. F. Weber.[1] This list, although by no means complete, is sufficiently elaborate to be used as a first place of reference for determining whether or not any given agent has previously caused dermatitis. The value of the work is enhanced by a second list, which groups the substances under the occupations in which they are encountered. Several hundred substances are recorded. It seems that the value of this work would have been further increased if the author had been able to distinguish between those substances in which satisfactory proof of causation had been scientifically established, and those substances which are reported merely as presumptive causes. A further improvement would have been the distinction between those substances which produce dermatitis because of their intrinsic damaging properties (primary irritants), and those substances which are not intrinsically irritating to the skin but which may produce hypersensitivity, and thus allergic contact dermatitis.

L. Schwartz,[2] of the Office for Dermatoses Investigation of the U. S. Public Health Service, has published a second monograph on Skin Hazards in American Industry. This work reports investigations of

causes of dermatitis in the following occupations, for example: (1) The manufacture of synthetic rosins and waxes; (2) the manufacture of leather; (3) the processing, tanning, and dyeing of furs; (4) the manufacture of artificial silks; (5) the dyeing of fabrics (and dermatitis resulting from exposure to dyed fabrics); (6) the manufacture and use of insecticides and fungicides.

The details and results of these investigations are too numerous and too complicated to be summarized here. However, they bring clearly to light the incalculable complexity of modern manufacturing processes. These processes often lead to exposure to so many different agents and intermediate substances, that the problem of discovering the actual causative factor of occupational dermatitis may, in many instances, be impossible; or, in other cases, be possible only at the hands of an expert after painstaking, personal analysis of the entire process at the site of manufacture.

In a second publication, L. Schwartz and C. D. Hocker[3] furnish an excellent illustration of the fact that intermediate substances, produced during a manufacturing process, may cause dermatitis when all the original substances are without eczematogenous properties. Cable splicers, suffering from dermatitis, were found to be sensitive to some irritant evolved during the "boiling out" operation, which involves heating to over 400° F. a mixture of oil, paraffin, and a dye. In this investigation, the separate ingredients used in the process were exonerated as causes of the dermatitis. Apparently, some alteration of, or conjugation with, the dye molecule was responsible for the sensitization.

The above fact calls to mind two important well-known observations: first, that dye intermediates (such as, for example, dinitrochlorbenzol and dinitrosomethylaniline) are strong, if not obligatory, sensitizers (see last year's review), while the finished, pure dyes derived from these intermediates may have lost, to a great degree, their sensitizing properties; and second, that relatively simple, small molecules, such as dyes, may act as *haptens,* and, as shown in the brilliant work of Landsteiner and collaborators, may assume sensitizing properties and full antigenic and anaphylactogenic properties by conjugation with larger molecules, such as proteins; or, in this instance, perhaps with oils (lipoids). The sensitivities and antibodies produced by such newformed "complex antigens" are then of a specificity determined not by the larger component, but by the smaller, simpler chemical, which acts as a so-called "partial antigen," or *hapten.*

In continuation of their experiments with sensitization to simple chemicals, Landsteiner and Jacobs[4] were able to adduce further support to the Wolff-Eisner hypothesis (1907). These investigators showed that injections of 1, 2, 4 trinitrobenzene regularly sensitized guinea pigs' skins, while no sensitivity was produced when 1, 3, 5 trinitro-

benzene was injected in the same manner; and that this difference in biologic effect of various Cl and NO_2 substituted benzenes paralleled their ability to form substitution compounds with an organic base (anilin).

It is obvious that the ability to form compounds with anilin may be associated with an ability to form compounds with certain proteins or protein split products. In this event, the results of Landsteiner and Jacobs are in entire conformity with the Wolff-Eisner hypothesis, and it may be assumed that, in the instance of at least the simple chemicals investigated, the sensitization is probably due to the formation of compound antigens with the animal's own larger molecules (proteins).

Fierz, Jadassohn, and Stoll,[5] working with the Schultz-Dale technic, were able to adduce supportive evidence for the theory of the in vivo formation of such a compound, by showing that the uterine strip of guinea pigs sensitized to a complex antigen reacted not to the simple chemical alone, but to the simple chemical conjugated with either heterologous or homologous protein.

Not only in drug eruptions, but particularly in allergic eczematous contact dermatitis it has been striking that the causal allergens are, more often than not, simple chemicals, such as dyes, formalin, mercury salts, nickel salts, etc.; and the Wolff-Eisner hypothesis, that the sensitizing action of simple chemicals occurs through conjugation of simple chemicals with autochthonous protein, is theoretically applicable to contact dermatitis as well as to drug eruptions. However, the proof is still lacking that such a conjugation of a simple chemical with body protein must actually take place in the genesis of allergic contact dermatitis of eczematous type. It is wholly plausible that some other mechanism may be involved in the contact dermatitis type of sensitization, as it is well known that contact dermatitis, while certainly based on allergic sensitization, nevertheless differs in many important ways from classic anaphylactic urticarial, tuberculin, and drug sensitizations.

However, Haxthausen's[6a] recent and as yet unconfirmed work indicates that when a simple chemical such as a mercury salt is mixed with a foreign protein such as horse, sheep, goat, or pig serum, the injection of this mixture into human beings produces an eczematous hypersensitivity to mercury with much greater ease than does an injection of mercury alone. There are several remarkable findings in Haxthausen's studies. The first is that only some eczematogenous substances were capable of producing this deliberate experimental sensitization, while other clinically equally eczematogenous substances did not do so. Second, it is remarkable that foreign sera served successfully as the larger molecular component of the sensitizing mixture or

combination, while human serum (autogenous serum) did not act in this manner. (See Editorial, The Year Book of Dermatology and Syphilology.)[7]

Haxthausen's[6b] work further demonstrated that proteins from Monilia, Staphylococci, etc., could replace the foreign sera and act successfully as the larger molecular constituents of sensitizing mixtures. This led to the hypothesis that Monilia, Staphylococci, and other microorganisms on the skin surface may furnish the foreign protein hypothetically necessary for establishing skin sensitization to simple chemicals. In support of this hypothesis, Haxthausen points out the ease with which patients with seborrheic dermatitis, with its rich skin flora of fungi and bacteria, can become sensitized to applied mercury, etc.

I, myself, can testify to the unpleasant ease with which many cases of seborrheic dermatitis become sensitized to the mercury and other constituents of therapeutic ointments; but I believe that while this sensitization may perhaps be due to the presence of protein of foreign microorganisms, Haxthausen's explanation is not necessarily the only nor the proved one of the phenomenon observed.

It is quite extraordinary and, as yet, inexplicable, that in Haxthausen's experiments certain substances should have been able to sensitize when mixed with foreign protein, while other, closely related eczematogenous agents did not produce such sensitizations. The comparison of his results with nickel and cobalt is particularly interesting. Just as was to be expected from the close chemical relationship of these two metals, they possess strong immunobiologic similarities. In another study of Haxthausen's[8] it is shown that there are crossed immunologic patch test skin reactions in many cases of acquired eczematous sensitivity to nickel and to cobalt.

Yet, in spite of this apparent and demonstrable close similarity in the sensitizing properties of these two metals, in the deliberate experimental sensitizations nickel and foreign sera mixtures sensitized regularly, while cobalt plus foreign serum was incapable of producing hypersensitivity.[6]

Bonnevie's[9] studies demonstrated that eczematous hypersensitivity to nickel is as common as mercury hypersensitivity; and he called attention to the now well-known fact that eczema from nickel occurs not only in nickel platers, but also in wearers of nickel-containing metals (garters, spectacle frames, etc.).

The results in a series of skin tests in 2,000 patients are reported by Zündel.[10] This statistical compilation is rendered difficult to interpret because the author does not distinguish clearly between contact and atopic dermatitis, nor between patch tests and scratch tests. Foods, hair, and feathers are listed high among the causes of "eczema." It is obvious that this result is possible only where large numbers of

patients with atopic dermatitis are included in the eczema group; for all investigators are in agreement that the contact type of dermatitis is not characterized by a high incidence of positive immediate wheal reactions to food and inhalant proteins.

Among the eczematogenous agents which have been studied recently, a place of importance must be accorded to dyed fabrics of clothing, as reported in 15 cases by Bonnevie and Genner,[11] and in 3 cases of home-dyed underclothing by Chipman.[12]

I have been struck, both in private practice and at clinics, by the recent apparent increase in the numbers of cases of this type. The predominantly periaxillary and cubital localizations of eruptions due to dresses (clothing dyes), the entire history and appearance of these patients is usually suggestive;* but the final diagnosis rests upon both the positive patch tests with the suspected materials, and the amelioration of the dermatosis on avoidance of exposure.

Not only dyes in clothing, but also dyes in cosmetics have been reported as causing trouble. For example, Sézary, Horowitz, and Genet[13] have contributed a case history of cheilitis due to lipstick, in which they implicate a dye.

Dyes in lipsticks, rouges, powders, nail polishes, etc., and in articles of clothing, such as shoes, socks, suits, dresses, underwear, wrist watch straps, etc., have all been proved as causes of obstinate cheilitis, or of allergic contact dermatitis in many of my recent cases.

One of the latest additions to the list of dyed substances which may be capable of producing dermatitis, is contained in the article by Traub, Gordon, and van Dyke,[14] who report two cases of "dermatitis from dyed and otherwise treated citrus fruits." However, the authors did not prove that the dye caused the dermatitis in either of their two cases; for, in the first patient, undyed California orange rind apparently produced stronger patch test reactions than did the dyed Florida rind; and, in the second case, no patch test results with dyes alone were reported. In this latter instance, skin reactions were elicited not only by orange rind, but by ostensibly undyed lemon and grapefruit rind as well.

The proof that artificial orange dye is the actual cause of a given dermatitis is rendered extremely difficult by the following facts, among others: (a) the natural constituents of the rinds of citrus fruits are capable of sensitizing and producing dermatitis;[15] (b) it is known that citrus fruit peels contain primary irritant substances (oils, pinenes, etc.) which are liberated when the peel is crushed on the skin, and which may produce positive patch test reactions on normal skins. (This statement is confirmed in the control experiments of Traub and his collaborators.)

*My patients have almost all been stout women with a tendency to profuse perspiration.

Moreover, dyed oranges are usually subsequently covered with a waxy coating, so that in patch testing one cannot be certain of achieving sufficient contact of dye with the skin, unless one removes the waxy film or breaks the wax by crushing the peel. Traub and his collaborators exercised praiseworthy conservatism in their conclusions, and it is evident that, while theoretically, dyes undoubtedly may cause dermatitis, nevertheless, a more thorough investigation on additional cases will be necessary to establish artificial orange dye as a proved cause of dermatitis venenata.

In eruptions produced by fruits, not only do the sensitizing properties and the primary irritant properties merit consideration, but also the possible presence of photosensitizing agents must be borne in mind. Certain citrus fruits in all probability contain such photosensitizing agents, as becomes evident in the consideration of so-called berlock dermatitis. In the production of this dermatitis, bergamot oil plus sunlight form the causal combination. A similar situation apparently exists in the production of *dermatitis bullosa et striata pigmentosa* from fig trees, and other types of dermatoses produced by figs. The studies of Popoff and Zaharieff,[16] and of Kitchevatz[17] have served to elucidate the etiology of fig dermatitides. The latter author was able to show that the juice of the white layer, the rind, and the green leaves of the fresh fig, photosensitized the skin of all test individuals, and produced the characteristic lesions. While the lesions of the fig dermatitis resemble those of berlock dermatitis, the fig tree dermatitis resembles other photosensitization plant dermatitides, and particularly *dermatitis striata pratensis* and *dermatitis phytogenes striata,* which are due, in some instances, to other plants. (*Euphorbia,* etc.) These latter cases are often called *meadow grass dermatitis.* E. F. Corson[18] has reported a case with an extensive eruption, in which both sensitization and photosensitization were apparent factors in the production of the characteristic bizarre and linear lesions.

In his studies in adhesive tape dermatitis, Grolnick[19] alludes to the two types of reactions which I have mentioned in discussing patch tests with orange peel, i.e., the common one, due to the intensive and primarily irritating action of the ingredients, and the infrequent dermatitis based upon true allergic sensitization. He suggests the use of cellophane and collodion, etc., when patch testing cases of allergic adhesive hypersensitivity.

Unusual substances reported as causes of contact dermatitis include a menstrual pad by Cormia;[20] goat hair by Kile;[21] chicken blood by Newton;[22] and dust from dictaphone cylinders by Templeton and Allington.[23]

In performing patch tests with soaps, just as is the case in patch tests with the peels of citrus fruits, with adhesive plaster, etc., it is

often difficult to distinguish between allergic hypersensitivity and intrinsic irritant properties (in the case of soaps the primary irritant effect is usually considered to be due to the alkali).

In extensive studies with soap patch tests on 115 individuals, with 10 different soaps, Jordon, Walker, and Osborne[24] came to the conclusion that dilutions of 1:100 or 1:400 were suitable for testing to demonstrate hypersensitivity. These investigators state that, contrary to the current belief, it was not the alkali, but some other factor such as, for example, fatty acid which was responsible for the majority of the reactions they observed.

Some of the difficulties in the interpretation of patch test reactions are further illustrated by instances of localized sensitivity, in which the causal substances produce no reaction when applied as patch tests to areas other than those affected.

An interesting case of this sort has been reported by Hollander.[25] A patient presented a dermatitis of the penis, which occurred only during the hay fever season. Ephedrine, applied to the arm as a patch test, produced no reaction. There was no dermatitis about the nose, despite the fact that an ephedrine-containing nasal spray was being used by the patient. However, spraying the penis with a 1:50 solution of ephedrine reproduced the acute local dermatitis, and the discontinuance of the nasal spray led to permanent freedom from the penile eruption.

A somewhat similar demonstration of the local variation of sensitivity was reported by Field and the reviewer.[26] In the case of an adult experimentally sensitized to poison ivy, all the tested areas of the integument reacted to patch tests with poison ivy extract, with the notable exception of a circumscribed area on one forearm, which remained non-sensitive to repeated testing during the observation period of over one year. In this case, there were also marked chronological variations in the sensitivity, as demonstrated by repeated testing with quantitative dilutions. The authors point out that these apparently spontaneous fluctuations present factors of error which must be considered seriously in the evaluation of patch test results.

As a result of their experiment with the injection of acetone extracts of poison ivy, Blank and Coca[27] conclude that this method can establish a complete immunity to the usual direct contact with the plant in at least a considerable proportion of susceptible persons. In three groups of apparently similarly exposed workers in CCC camps, 66.6 per cent of the control group developed poison ivy dermatitis; whereas, of 45 men who received a total of 2 c.c. of a 0.1 per cent extract, only 20 per cent developed poison ivy dermatitis; and in a third group of 40 men receiving a total of 4 c.c. of a 0.66 per cent extract, only 7 per cent developed ivy dermatitis.

Memmesheimer[28] calls attention to the rôle of foci of infection in the genesis of skin sensitivity to eczematogenous agents, as well as to the influence of such foci on already existing hypersensitivities.

It is well known that hematogenously distributed products emanating from a distant infected focus may exert profound effects upon skin lesions which are actually directly attributable to exposure to other agents. This type of observation demonstrates that the effects of foci of infection may be based upon a nonspecific activation of skin lesions of other and varied etiologies. As mentioned last year, an analogy to this nonspecific activating effect may be found in the Schwartzmann phenomenon, in which dormant, nonmanifest, cutaneous alterations, produced by the injection of certain so-called "skin preparatory factors," become manifest only when an "eliciting factor," which may be of an entirely different nature, is brought to the prepared skin site via the blood stream.

Not only can internal factors "condition" the skin for the production of manifestations of hypersensitivity, but it has become more and more apparent that the reactions of cutaneous hypersensitivity can result in alterations in internal organs. Among the alterations which have been found to be associated with artificially produced dermatitis in animals, are those of the bone marrow, the liver,[29] the spleen and the adrenals,[30] and of many other organs.[31] These findings emphasize the necessity for great care in attributing a causal relationship to any changes in internal organs which are found subsequent to the onset of the dermatosis.

2. ATOPIC DERMATITIS

The reports of investigations since last year's review have, in general, served to make even more apparent the validity of the differentiation between contact dermatitis and atopic dermatitis. Considerable space was devoted to this differentiation last year, and it therefore seems unnecessary to mention the details here.

Obermayer, Becker, and collaborators,[32] Brunsting,[33] and Goodman and the reviewer[34] are in complete agreement on the basic principles in the differentiation of these two important types of allergic dermatitis. However, while Obermayer and his coworkers are inclined to question the clinical significance of the many positive wheal reactions to food and inhalant proteins, and even go so far as to interpret them as a purely functional phenomenon demonstrating a "protoplasmic instability," Goodman and the reviewer believe that the wheal reactions are specific, and demonstrate the allergic nature of the dermatosis. Nevertheless, Goodman and the reviewer, as well as Brunsting, are in complete agreement with Obermayer and his coworkers, that there is an uncertain degree of correlation between the specific urticarial skin test reactions and the clinical skin manifestations. It has

been emphasized in all three articles referred to that the elimination of the substances which produce the skin test reactions often fails to bring relief to patients with atopic dermatitis. Moreover, the employment of the skin-reaction-eliciting substances for specific desensitization is unfortunately almost always unsatisfactory in atopic dermatitis. Nevertheless, in an occasional case in adults, and in more numerous cases in children, and still more frequently in infants, the elimination of certain food and inhalant allergens (whether positive or negative on skin test) proves of decided benefit.

Brunsting (loc. cit.) reports 10, and the reviewer,[35] 2, cases of juvenile cataract associated with atopic dermatitis and evidently attributable to the same underlying allergic mechanism. Preceding these reports, Ruby Daniels[36] discussed in detail this association of cataract and atopic dermatitis. These apparently allergic reactions in the lens may be analogous to the now well-known cataracts caused by certain drugs which possess a strong tendency to sensitize, such as, for example, dinitrophenol.

3. URTICARIA AND URTICARIAL REACTIONS TO SKIN TESTS

From a perusal of the literature, together with personal communications from allergists and dermatologists, it seems more and more evident that routine skin testing with even the longest list of common food and inhalant allergens is not likely to be of aid in elucidating the cause of the majority of cases of urticaria. Moreover, the family history, the personal history, and the results of other investigations fail to justify the inclusion of most cases of acute or chronic urticaria in the group of classic atopic diseases.

As usual, many cases of urticaria due to drugs have been reported during the past year. It becomes increasingly apparent that the possible drug etiology warrants the most careful consideration in all cases of this dermatosis. In some cases, the eliciting drug produces wheal reactions on skin test; but, in the majority, such reactions are not found. However, most authors agree that, even with the strongest urticarial reaction to skin test, no passive transference reagins are demonstrable. (See the discussion of aspirin sensitivity, which appears in the section on Drug Allergy.) In spite of previous reports to the contrary, it now becomes apparent, as reported by Hitch and Schwartz,[37] that dinitrophenol is no exception to the above rule; and that, in this instance just as in most other urticarial drug eruptions, the earlier reports of successful passive transference were based on technical and other errors.

Tuft and Brodsky,[38] in interesting studies of the effects of drugs on skin reactions to allergens, demonstrated that the effect in reducing the size of the skin test reaction ran fairly well parallel to the efficacy of the respective drugs in the treatment of "allergic conditions."

Thus, adrenalin and related drugs proved to be the most effective inhibitors, while calcium and sodium iodide had no inhibitory effects.

It is well known that microorganisms can produce sensitizations of various types, including urticarial skin responses. The rôle of pathogenic microorganisms and their products in the production of urticaria and of atopic dermatitis merits consideration in those numerous cases in which other allergens cannot be proved to be responsible. (See above, section on *atopic dermatitis.*) Pathogenic fungi of the trichophyton group have been proved to be capable of producing urticarial skin hypersensitivity, and of eliciting the formation of specific reagins. The same applies to the monilia organisms (the reviewer, Ramel and Benziger, and others). The report of Biederman[39] makes it evident that not only pathogenic fungi, but also ordinary yeasts may be responsible for urticaria (and angioneurotic edema ?). It is of interest that sensitization in certain of this author's cases followed massive exposure to yeast by the ingestion of cakes of fresh yeast, and that patients, once thus sensitized, became intolerant to even the smaller quantities of yeast in bread and other baked foods. In the cases reported, the skin test to a 1:1,000 dilution of yeast extract gave positive wheal reactions, and the elimination of the yeast-containing foods gave prompt relief.

Chevallier and his coworkers[40] have contributed a series of studies in which they report that the disease urticaria is not confined to the skin, but is accompanied by changes in the gastric mucosa, which vary from acute edema, visible in the gastroscope, to true atrophic gastritis. These authors state that urticaria may be a systemic disease occurring in each and any of the viscera which possess connective and vascular tissue (see also Reference[43]). A number of disease conditions have been explained on the basis of angioneurotic edema involving the nervous system (migraine and epilepsy); the bladder mucosa or the urethra (anuria or hematuria); and the heart (pulmonary edema and paroxysmal tachycardia). Internal urticaria may exist with or without skin manifestations. When this type of reaction occurs in the stomach, the patient complains of gastric disturbances; and the gastroscopic examination reveals urticarial lesions and swellings of the mucosa.

This concept, of course, corresponds to the usual one. The sensitivities of urticarial type are by no means confined to the skin, but the viscera may also participate and be shock tissue, with or without concomitant skin involvement. This same conception is applicable not only to urticaria, but also to skin purpuras on an allergic food or drug basis, and to their common association with visceral manifestations most frequently localized in the gastrointestinal tract (Henoch-Schönlein purpura).

Among the etiologic agents other than allergens to which urticaria is attributed, one may add to the well-known physical urticariogenic agents, such as light, cold, heat . . . ; and to this list one can now append the case of urticaria attributed to x-ray by Giardina.[41]

It is interesting to note that it has recently been demonstrated that the simple intracutaneous injection of certain photosensitizing substances produces no urticaria, but that a wheal appears at the site of the injection upon subsequent exposure to ultraviolet light.[42]

A practical review of the approach to the treatment of acute and chronic urticaria will be found in the introductory article to the Year Book of Dermatology and Syphilology for 1936.[43] This article briefly mentions certain aspects of etiologic diagnosis, of skin testing, and of elimination of allergens which may prove of interest to the practicing allergist.

4. DRUG ERUPTIONS

In those drug eruptions which are based upon sensitization mechanisms, and it is probable that the majority of drug eruptions are on this basis, the usual toxicologic methods of study are of little value, particularly since amounts of drugs too small for chemical detection are still capable of producing severe eruptions. Fatal iodo- and bromodermas from small quantities of these drugs have been reported, so that even the amount of iodine in "iodized salt" may be a serious menace to health. Bloch and Tenchio (see last year's review) reported fundamental studies on a case of fatal bromoderma. This year, Goldstein[44] adds the eleventh reported case of fatal iododerma; and Hollander and Fetterman,[45] the twelfth. Goldstein's case was due to the injection into the lung of iodized oil for diagnostic purposes; while the case of Hollander and Fetterman followed the ingestion of yellow mercurous iodide. The investigation of the latter case showed that, even in a fatal iododerma occurring in a patient known to have been taking iodides, repeated examinations of the urine may consistently fail to reveal iodine. The type of histologic change demonstrated in this case is also worthy of note, in that the inflammatory process, while of granulomatous character, in some stages resembled the alterations seen in neoplasms.

In eruptions suspected of being due to arsenic, the demonstration of arsenic in the urine is of even less value than in eruptions due to other drugs; for, exposure to, and absorption of, varying amounts of arsenic is universal today. The normal arsenic content of the urine fluctuates over a very wide range, and the finding in the urine of even subnormal amounts does not exculpate arsenic as a cause of an allergic dermatitis. On the other hand, a high arsenic content of the urine does not necessarily demonstrate the causal rôle of arsenic; for, individuals without skin sensitivity to arsenic may excrete large amounts of this metal over long periods of time without presenting any skin

changes. Not only does the subject of arsenic excretion require further study, but a revision of the prevalent loose ideas in regard to its diagnostic significance is apparently necessary.

It seems that still another fallacy regarding arsenic excretion has been uncovered by Mattice and Weisman,[46] who once again demonstrated that the excretion of arsenic in normal subjects shows very great variations from day to day, according to diet, environment, topical applications, and to other usually uncontrollable factors; and also, under controlled conditions, that, far from increasing arsenic excretion, the administration of sodium thiosulphate actually decreased the urinary output of the metal. Inasmuch as no satisfactory clinical proof of the efficacy of sodium thiosulphate in the therapy of arsenical dermatoses has been adduced, it would seem that, in the light of these new experimental findings, the drug may actually do harm rather than good.

The allergic nature of the so-called arsenical dermatoses is well illustrated by the fact that they are due, more often than not, to a complex radical containing arsenic, rather than to the element itself. Thus, patients sensitive to arsphenamine can often tolerate a pentavalent organic arsenical, such as tryparsamide, or an inorganic arsenical such as Fowler's solution.

While dermatitis has usually been caused by the trivalent organic arsenicals (arsphenamines), it has been shown that tryparsamide is also a sensitizing complex, as demonstrated in the report by Robinson[47] of dermatitis due to this drug.

Occasionally there is even a crossing of allergic hypersensitivity, so that patients, sensitive to one arsenical, will react to several or to all others. Pillsbury's[48] case of fixed arsenical eruption demonstrates such crossed reactions in a patient in whom the same areas were sensitive both to tryparsamide and to silver arsphenamine. The apparent synergistic action of the two drugs in this case once more calls to mind the Schwartzmann phenomenon and the nonspecific preparation of skin sites (see above).

Moreover, the well-known nonspecific effects which certain substances exercise in producing flares of skin sites in which an unrelated substance had been deposited previously, has once more been confirmed by Cormia.[49] This author showed that in guinea pigs' skins the sites of old deposits of neoarsphenamine flared up when staphylococcus toxin was injected at a distant site.

As previously mentioned, some cases of purpura hemorrhagica may now be regarded as typical manifestations of specific drug hypersensitivity. Many authors have reported thrombocytopenic purpuras due to various drugs, including notably barbiturates, sedormid, gold salts, and the arsphenamines. Falconer, Epstein, and Wever[50] give a brief review of the literature of the purpuras, and add 3 cases of pur-

pura hemorrhagica following neoarsphenamine. It is interesting to note that they were able to demonstrate a definite specificity of this hypersensitivity, which in all 3 cases was directed toward the neoarsphenamine radicle. There was no demonstrable sensitivity to arsenic as potassium arsenite, sodium cacodylate, tryparsamide or mapharsen, and no sensitivity to the radicles of these drugs (see above).

Dinitrophenol has already been mentioned as a cause of drug eruptions of urticarial and angioneurotic type (see section on Urticaria and urticarial skin reactions[37]). This drug also produces other forms of skin eruptions, as well as cataracts and severe and even fatal blood dyscrasias. From the statistical evidence available, and from the type of dermatoses produced, it would seem that the ill effects of the drug are based upon allergic hypersensitivity. Dinitrophenol is, apparently, one of the drugs which frequently sensitize. It will be recalled that drugs range from those which sensitize few if any individuals, to those which sensitize almost 100 per cent of those exposed. "Nirvanol," a hypnotic which has been widely used in the treatment of chorea, is perhaps the best example of this latter category; for, practically all individuals to whom Nirvanol is administered in therapeutic doses develop a uniform type of allergic disease with fever, a rash, and other symptoms almost identical with those of serum sickness. In this example, the allergic mechanism is apparent, not only in the striking analogy of the incubation and manifestations to those of classic serum sickness, but also because of the sharp specificity, as demonstrated by ingenious experiments with the separate dextro- and levo-stereo isomers of phenyl-ethyl hydantoin (Nirvanol is the racemic mixture), which were performed by Sobotka, Peck and Kahn[51] some time ago.

Nirvanol disease is a condition worthy of study from the allergic viewpoint. It seems possible that investigations with this well-defined chemical allergen may throw further light on the phenomena and mechanisms of the type of sensitivity represented by serum sickness. Those interested in this subject are referred to the excellent summary by Madden.[52]

Prickman and Buchstein[53] have reviewed the subject of aspirin hypersensitivity, and added their observations in 62 cases of this condition. Urticaria and angioneurotic edema, together with asthma, are the most common manifestations of reaction to the ingestion of aspirin by hypersensitive individuals. It is particularly noteworthy that this form of drug hypersensitivity seems to be of atopic nature, since it occurs in association with asthma and other types of allergy (unspecified in the article). Nevertheless, while the skin test may occasionally elicit a positive reaction, no reagins to acetylsalicylic acid can be demonstrated.

I cannot agree with the statement of these authors, that "hypersensitivity to acetylsalicylic acid is the most common form of drug allergy. . . ." While I believe that hypersensitivity to aspirin may be

the most common drug hypersensitivity encountered in asthmatic or atopic individuals, certainly hypersensitivity to other drugs, such as bromides, iodides, barbiturates, phenolphthalein, and arsphenamine, is more common in the dermatologic material which I have observed; and, in all probability, is also more common in patients seen in general practice. In this connection it is to be emphasized that not only aspirin, but other drugs, and particularly those mentioned above, must be considered as possible causes in all cases of chronic urticaria and angioneurotic edema. It is regrettable that Prickman and Buchstein failed to distinguish sharply between atopy and other forms of allergy.

This brings out the point that the connection of various types of drug sensitivity with atopy requires further study. While it is probable that aspirin allergy is more likely to occur in atopic than in nonatopic individuals, there is as yet no proof that this holds true in allergy due to other drugs. This question and many other interesting aspects of drug allergy are admirably discussed in a recent review by Abramowitz.[54]

5. SKIN ALLERGY IN INFECTIOUS DISEASES

The interest in the Frei skin reaction in *lymphopathia venerea* has continued unabated. Among others, two general discussions of the subject, with additional observations, are submitted by Bacon[55] from Philadelphia, and by Prehn[56] from the Philippines. Both articles once more emphasize the almost absolute specificity and the diagnostic reliability of the Frei skin test; and further demonstrate the widespread geographic dissemination and relative frequency of the different manifestations produced by the *lymphopathia venerea* virus.

Prehn, moreover cites an unusual case which demonstrates that the skin reaction may not become positive until the disease has been in full development for a period of several months. This is surely an exceptional happening, for the Frei skin test is usually positive by the time the bubo softens, except in certain cases of coexisting florid syphilis.

Further studies with the mouse brain Frei antigen, recommended for diagnostic purposes by Grace and Suskind, have been submitted by the same authors,[57] who maintain, in contradistinction to the contention of Straus and Howard, discussed in last year's review, that the skin reaction is reliable if the interpretation of a positive reaction is strictly limited to a papule over 7 mm. in diameter. While final decision as to the correctness of either of these divergent opinions must await further experience with mouse brain antigens, it must be said that determination of a positive or negative tuberculin type of skin reaction by measurements of millimeters will surely be regarded as most impractical by all observers with wide experience in reading such reactions. Moreover, it is obvious that mouse brain antigen, containing mouse foreign protein,

may, in some cases at least, produce sensitivity; and that it is possible that some patients may be sensitive to mouse protein even before the test is performed.

It would appear that a normal mouse brain control, injected at the same time as the mouse brain antigen, would do much to eliminate the theoretic uncertainty of the present method of testing. For the present at least, it would be wise to employ such a control, and thus improve a method of testing which is of undoubted value in the numerous instances in which human Frei antigen is not available.

Tamura[58] reports that animals, treated with *lymphopathia venerea* virus, produce antibodies which neutralize Frei antigen. In testing the skin of 32 Frei positive *lymphopathia venerea* patients by means of the intracutaneous injection of anti-Frei-antigen goat serum, it was observed that 31 patients responded with an immediate papular and erythematous reaction (not urticarial). The author claims that the reaction is specific and independent of possible sensitivity to goat serum, and that it may be used as a rapid means of diagnosis. If and when confirmed, these studies will not only have provided another and easier means for the diagnosis of *lymphopathia venerea,* but also they will have opened up the prospect of treatment with antiserum. (At present the best method of immunologic treatment is the active method, by means of intravenous injection of small doses of human Frei antigen, as first used by Hellerström.) Tamura's work lends support to the possibility of using a new type of skin testing, developed by Foshay's studies,[59] in which an antiserum is reported to produce a specific immediate reaction (erythematous-edematous, but not a wheal) when injected into the skins of individuals infected by the organism with which the antiserum was prepared (E. E. reaction of Foshay).

The effects of skin allergy dominate the cutaneous manifestations of syphilis, and have again been the subject of numerous clinical and laboratory investigations.

Lisi[60] showed that, upon superinfection with a spirochete from a rabbit infected with syphilis, 13 of 17 patients with general paresis developed nodular reactions in which spirochetes could not be demonstrated, either histologically or by rabbit inoculation. In one case there resulted a lesion at the inoculation site and a generalized papular exanthem. These experiments confirm the finding that pareties have a skin allergy (specifically altered capacity to react) to spirochetes, demonstrable by reinoculation, an allergy which never permits the production of chancres, but which results in either no lesions at all, or in lesions of tertiary and very rarely of secondary type.

Just as the experiments with skin inoculations of tubercle bacilli in tuberculosis immune animals—e.g., the rat (W. Jadassohn)—have yielded valuable information concerning the rôle of allergy in tuberculoderms, just so has the infection with spirochetes of the syphilis-refrac-

tory mouse (Kolle, Schlossberger and others) thrown light on the rôle of allergy in syphilis. Infection of the mouse with *T. pallida* produces no lesions, either at the site of inoculation or elsewhere, and no manifestations of disease whatever. Recently, however, Stroesco and Vaisman[61] have found that dark-field and histologic examinations of the infected mouse reveal numerous spirochetes in the skin and in the internal organs, with the exception of the walls of the digestive tract and the striped muscle. It is apparent, therefore, that no allergic hypersensitivity (and no resistance) to the spirochete occurs in the mouse. This animal thus remains without disease in spite of the fact that it contains such large numbers of organisms. It may perhaps be considered the best culture medium for the *T. pallida.*

Levaditi and his collaborators[62] have also demonstrated rapid dispersion of *T. pallida* from the skin inoculation site in the naturally immune nonallergic tissues of the mouse; whereas, in the susceptible (allergic) rabbit, guinea pig, chimpanzee, and human being, no general cutaneous dissemination of organisms occurs after local skin inoculation. In the skin of these latter animals the treponema is found only at the site of actual lesions.

In leishmaniasis, skin tests have been performed and specific reactions have been noted. While Mayer and Malamos[63] found that there was some degree of crossed reaction between strains of *Leishmania* from Kala azar (*donovani*) and strains from the Oriental boil (*tropica*), they also found that there was a certain degree of specificity in the skin test reaction to these two vaccines, in that *leishmania tropica* vaccine produced a higher percentage of reactions in patients with Oriental boil, while *leishmania donovani* vaccine produced a higher percentage of reactions in individuals with Kala azar.

These findings are in strict analogy to the demonstrated immunebiologic relationships and differences, as shown by antigen analysis of trichophyton fungi, brucella bacilli, etc., by W. Jadassohn and his coworkers (see last year's review).*

In regard to allergy to pyogenic organisms, several authors have discussed the possibility of the existence of "bacterids" in the form of pustulo-vesicular eruptions on the hands, of rosacea, and of other types of dermatoses.[64] In my opinion, none of these investigators has succeeded in demonstrating that the cases under investigation were actually "ids." While it cannot be denied that cases of "bacterid" nature may exist ("Microbids" of Bloch), and while the hypothesis may prove fruitful, nevertheless, the clinical and laboratory evidence which has been required to establish the concept of the tuberculids and the trichophytids is, as yet, almost entirely lacking in the instances of these so-called "bacterids." The main evidence adduced in these newer con-

*Since the preparation of this review, another article on this subject has appeared. (*W. Jadassohn, Schaaf, and Wohler,* J. Immunol. 32: 203, 1937.)

tributions is the observation of amelioration or cure of skin lesions, following the removal of distant foci of infection. While it is true that these foci may have acted as sites from which material was being disseminated to produce specific "ids," it must also be borne in mind that some of the improvement may have been *post hoc* rather than *propter hoc;* or, that presence of the focus may have contributed, in some nonspecific way, to the existence of the skin lesions. (In this connection, see the discussion above of the paper by Memmesheimer,[28] and of the Schwartzmann phenomenon, in the section on *Contact Dermatitis.*)

Touart, Thomas and Tucker[65] have shown that, in individuals who by skin tests have been demonstrated to be hypersensitive to vaccines of pyogenic organisms, the repeated intracutaneous injection of these vaccines reduced the size of the papular forty-eight-hour type of reaction. However, when an immediate wheal type of reaction to these vaccines existed, the reduction of this form of response could not be accomplished. These results with staphylococcus and streptococcus vaccines merely confirm the well-established results of other investigators with trichophytin, tuberculin, oidiomycin, foreign sera, etc.

G. Rubin and the reviewer[66] demonstrated that repeated injections of staphylococcus toxoid in man reduced the skin susceptibility to staphylococcus toxin, and also the skin sensitivity to toxoid. The reduction of the reaction to toxoid is, in all probability, analogous to the above mentioned hyposensitization with vaccines and fungus extracts. The results of this form of therapy are promising in certain pyodermas in which sensitivity to staphylococcus products seems a major factor.*

From the studies of the French school (Ramon, Gerez, Boccage, and coworkers), as well as those of J. Ferguson Smith,[67] it becomes apparent that the cutaneous therapeutic effect which may be exercised by staphylococcus toxoid injections is not necessarily based upon circulating antitoxin.

Observations in many other infectious diseases, and now in staphylodermas, lead to the concept that the disease manifestation may be due either to toxin effects or to sensitization to products of the microorganisms other than toxins, or to a combination of both. Therefore it is now most logical immunologically to combat staphylodermas by using "desensitization" or "hyposensitization" procedures (vaccine or toxoid) combined with procedures designed to produce antitoxic immunity (toxoid, toxin, antitoxic sera).

Forman[68] has reported on the effects of the use of staphylococcus toxoid on sycosis vulgaris. His results were, on the whole, unsatisfactory. Bearing out what has just been stated, he noted that clinical improvement did not necessarily run parallel to blood antitoxin content.

I have found that there is a great and, at present, inexplicable vari-

*In as yet unpublished studies of G. Rubin and the reviewer, Staphylococcus Toxoid proved a highly valuable therapeutic weapon in (1) folliculitis of the scalp; (2) acne varioliformis; and (3) some cases of cystic acneform dermatoses.

ability in the responses to staphylococcus toxoid injections: some individuals readily develop antitoxic sera of high titer, and others show no increase in titer, in spite of the persistent administration of large doses.

G. Rubin and the reviewer[69] have a found that the subcutaneous injection of toxoid is more effective than is the intracutaneous administration, in raising the blood antitoxin titer.

This brings out the point that the various possible methods of administering vaccine, toxins, and toxoids require further study.

One such recent study has been performed by Ishikawa[70] with the percutaneous administration of staphylococcus vaccines. These were rubbed into the skin of rabbits, in the form of a lanolin ointment. It was found that there was percutaneous penetration which produced not only an increase in the antibody content of the blood, but also a marked increase in the resistance of the skin to staphylococcic and streptococcic infection.

The rôle of sensitization to products of the streptococcus, in the production of the local and general manifestations of erysipelas, forms the subject of a communication by Gastinel and Reilly.[71] These observers incline to the opinion that the manifestations of erysipelas are principally based upon specific sensitization to streptococcus products, rather than upon the direct effect of the streptococcus toxin. They cite observations both in human beings and in animal experiments in support of this concept.

The well-known tendency to recurrences and the predilection for repeated involvement of the same site are obviously more easily understood on the basis of hypersensitivity than on that of toxin effect.

6. TRICHOPHYTIN AND TUBERCULIN ALLERGY

In last year's review, it was mentioned that the therapy of trichophytids by means of hyposensitizing injections with trichophytin was theoretically sound but unfortunately, as yet, of little practical value. An attempt to improve the practical results is to be found in the preparation of a new, polyvalent and denatured Brazilian "claso-vaccine," which was discussed in last year's review. During the past year, there have been both favorable and unfavorable reports on the use of this product.

My own, rather limited, experience has not convinced me of the superiority of this newer "claso-vaccine" over the older forms of trichophytin. While most cases of presumptive dermatophytids unfortunately prove refractory, an occasional striking result will be produced by this therapy when other measures have failed. This parallels experience with other trichophytins.

Among the allergic manifestations which have been attributed to the products of fungi, including the Trichophytons, Epidermophytons, Monilias, yeasts, and molds, one may list, in addition to the usual cutaneous "ids," the manifestations of asthma, vasomotor rhinitis, con-

junctivitis, urticaria, erythema nodosum, erythema multiforme, lymphangitis and lymphadenitis.[72] A somewhat different form of possible trichiphytid has been discussed by Charles M. Williams, and has been studied more recently by Traub[73] and by the reviewer.[74] In the cases referred to, recurring erysipelas-like eruptions appeared on the legs in the presence of demonstrable fungus infection on the feet. The clinical, bacteriologic and immunologic findings incriminated fungus products rather than the products of streptococci. From the viewpoint of the allergist, it is particularly noteworthy that in these cases the forty-eight-hour type of reaction to trichophytin may be absent, while the immediate wheal and flare reaction may be present. In some instances, reagins, specific to trichophytin, have been demonstrated in the sera of these patients. Summaries of the cases mentioned are available.[75]

The reader interested in the present status of opinion on the rôle of allergy in tuberculoderms is referred to the two summaries of recent date.[76] Bonnevie and With[77] have contributed newer studies on the results of quantitative tuberculin tests in tuberculoderms. In a large series of normal individuals, of patients with pulmonary tuberculosis, and of patients with tuberculosis of the skin, their findings have been on the whole confirmatory of those of Martenstein and Noll,[78] which were discussed in last year's review. There are at least two findings worthy of emphasis. First, Bonnevie and With found that their cases of tuberculosis indurativa and of tuberculosis papulo-necrotica were strongly hypersensitive, and did not tend toward the anergic or sarcoid group in their reactions. They attribute the slight discrepancy between their findings and those of Martenstein and Noll to the reading of all skin reactions, not only at forty-eight hours, but also at one week. This method of reading the tests disclosed more and stronger reactions. The second noteworthy finding was that the group of lupus vulgaris patients, which evidenced only moderately hyperergic skin reactions to tuberculin, was found to have a relatively high incidence of active pulmonary tuberculosis, as compared to the group of lupus cases with strongly hyperergic skin reactions to tuberculin. The authors draw the conclusion that in patients with lupus vulgaris the finding of only moderate cutaneous tuberculin hypersensitivity must make the physician suspect an active pulmonary focus.

A further proof of the dominant influence of the state of the allergic sensitivity of the skin on the course and morphology of tuberculoderms will be found in the investigations of Funk[79] on the virulence of tubercle bacilli recovered from the lesions of lupus vulgaris. This author, after careful and detailed bacteriologic studies, came to the conclusion that the resistance of the individual is the dominant influence. Even organisms which are relatively avirulent for the guinea pig can produce the severest forms of lupus vulgaris. It is interesting to note that Funk discovered that the allergic change is not confined to the macroorganism,

but is found in the microorganism as well; for, according to his findings, the longer the bacillus has been harbored in the lupus nodules, and the longer it has been subjected to the immunebiologic forces of the human host, the less virulent it becomes for guinea pigs.

An important moot question, and one which yearly receives its merited attention, is the problem of the rôle of tuberculin sensitivity as a possible factor in adequate resistance. Selter[80] is in agreement with the opinion expressed in last year's review. For, in a summary of the different interpretations of the rôle of tuberculin hypersensitivity, he comes to the conclusion that the deliberate reduction of this sensitivity is a logical therapeutic approach in tuberculosis. This is in agreement with the methods of repeated injection of small quantities of tuberculin, as practiced with some success in certain tuberculoderms. However, as Selter points out, the method is uncertain and not without danger. But it is essential to continue in this direction, and with the full realization of the future possibilities of specific hyposensitization measures in such diseases as tuberculosis, syphilis, leprosy, mycotic diseases, and in a great number of other chronic infections in which the most important manifestations may be based on hypersensitivity to products of the invading microorganism.

In view of these facts, measures which will reduce the tuberculin sensitivity of the infected organism cannot fail to hold interest. Some time ago, the reviewer and Oser[81] showed that cevitamic acid reduced the susceptibility of guinea pigs to arsphenamine skin sensitization of tuberculin type; and recently Steinbach and Klein[82] demonstrated that a similar influence could be found in regard to the guinea pig's tolerance to tuberculin.

It would thus seem that certain relatively large doses of cevitamic acid are capable of reducing the sensitivity of the guinea pig's skin in a general nonspecific manner. In this connection, it may be recalled that the earlier findings of R. L. Mayer and the reviewer have shown that a diet containing green vegetables reduced the skin reactions to sensitizing agents, such as arsphenamine and paraphenylendiamine.

In the immunology of tuberculosis, greater attention is being given, not only to the changes in the skin reaction to tuberculin, but also to the serologic alterations. In addition to studies with the anti- and pro-cutins, specific complement fixation reactions and other serologic tests are becoming of practical importance.

The Meinecke tuberculosis reaction, as investigated by Boas and Freudenthal,[83] and by Böhne,[84] seems to be a valuable serologic diagnostic measure. It appears to possess both sensitivity and specificity. In the first report,[83] 87 per cent positives were found in a series of 755 patients with active pulmonary tuberculosis; whereas only 3 positive reactions were found in 521 "nontuberculous" controls; and in these 3 positive reactors there was active tuberculosis in the immediate

family. The second report,[84] comprising the results of the investigation of 20,000 cases, demonstrates that the reaction is positive in cases with large areas of active pulmonary involvement; but that in extrapulmonary tuberculosis it is not infrequently negative. No special mention is made of the value of the Meinecke tuberculosis reaction in tuberculoderms.

A careful study of the possible correlation between the quantitative tuberculin skin test and the serology would now promise to yield information of value in reference to cutaneous tuberculosis.

7. POSSIBLE ALLERGIC FACTORS IN CERTAIN OTHER SKIN DISEASES

The rôle of specific hypersensitivity has, of late, received so much attention in all manner of diseases that it would be remarkable indeed if acne vulgaris had not been subjected to scrutiny from this point of view. It has long been recognized by dermatologists that, not acne vulgaris, but certain acneform eruptions are essentially due to specific hypersensitivity to certain drugs, such as iodides, bromides, and perhaps other sedatives; and to circulating substances originating from infectious foci (acneform tuberculids, etc.). Moreover, certain external irritants have long been known to be causes of acneform dermatoses (tars, oils, paraffins, waxes, grease, chlorine, chlorinated diphenyls and naphthols, wool, sunlight, etc.).

In addition to this, it may be stated that certain acne vulgaris cases exacerbate at certain times after the ingestion of certain drugs and foods (bromides, iodides, chocolate, etc.).

Recently, however, several authors, including Cunningham and Mendelhall,[85] have attempted to show that all acne vulgaris patients are food-sensitive, and that classic acne vulgaris is, in itself, essentially a manifestation of food allergy.

Since it is obvious today that acne vulgaris is an erratic disease of spontaneous remissions and, most commonly, with spontaneous cures, the therapeutic results of any new measure can be evaluated only by a large series of cases, and by seasoned dermatologists of conservatism, and of wide experience in the natural course of the disease. And all such qualified observers are in almost unanimous agreement that neither elimination diets, nor endocrinologic therapy, nor vitamins, nor any of the other newer measures, such as vaccines, staphylococcus toxoid, etc., have as yet proved to be of great value in the management of the general run of patients with ordinary acne vulgaris.

This does not imply that in exceptional cases, i.e., those which resist the usually highly effective dermatologic management (which includes a safe dosage of x-ray as the therapy of choice), all or any of the adjuvant measures just mentioned may not be of service. (In certain cystic acnes of older women [which is not acne vulgaris] staphylococcus toxoid has satisfied me as to its value.)

As previously and repeatedly pointed out, there can be little doubt that acne vulgaris is in some way related to the general endocrine status at puberty, and may be more particularly regarded as a follicular and pilosebaceous response to internal factors connected with gonadal secretion. Any theory, such as for example, that of food hypersensitivity, which leaves this concept out of consideration, seems doomed to fall short of satisfactorily accounting for the course and manifestations of acne vulgaris.

The skin as a test organ for demonstrating existing or pre-existing infections or internal sensitivities has long received almost universal consideration; but the use of skin reactions to demonstrate the existence of neoplasms is considerably more recent. B. Gruskin[86] investigated the use of intracutaneous testing with extracts of embryonic mammalian pancreas, of submaxillary glands, and of liver, in the diagnosis of carcinoma; and of extracts of Wharton's jelly, and embryonic bone marrow in the diagnosis of sarcoma. It is said that in positive cases "a slight area of inflammation with pseudopod formation appears within fifteen minutes." Both the interesting theory and the question of diagnostic usefulness of the Gruskin test are of manifest importance. While some confirmatory reports have appeared (Bacon,[87] Bacon and Murray,[88] Pratt[89]), it will require many more years of intensive investigation to establish the value of this skin test for malignancy.

The above remark applies to various skin tests which have recently been advocated for the diagnosis of pregnancy. (Tests with anterior pituitary, etc.; and the Gruskin test with placental extract.)[90] The final judgment on all these tests must await further confirmation of the reported satisfactory results.

8. ALLERGIC MANIFESTATIONS OF THE SKIN, WITH PARTICULAR REFERENCE TO THEIR SIGNIFICANCE IN GENERAL IMMUNOLOGY

In an excellent review, which should be read by all interested in allergy, W. Jadassohn[91] gives a detailed discussion of allergic mechanisms in general, and in particular of the analogies and differences between classic anaphylaxis, urticarial skin reactions, eczematous skin reactions, and allergic skin reactions, which are neither urticarial nor eczematous. He comes to the conclusion that there are many analogies between all of these forms of reaction. But, for the present at least, only the anaphylactic and the urticarial sensitivities can be considered to be closely related, in that they are both already proved to be mediated by antigen-antibody reactions. There is, as yet, no proof that eczematous hypersensitivity or other skin hypersensitivities of nonurticarial type are mediated by antibodies. For the moment, at least, these forms must, therefore, be considered to be distinct from urticarial and anaphylactic sensitizations. The author presents these and other differences and relationships in tabular form.

The mechanism of the genesis and spread of sensitivity has been studied by Lehner.[92] The intracutaneous deposit of substances producing urticarial hypersensitivity first leads to local hypersensitivity, then to hypersensitivity of the adjacent areas, and last to hypersensitivity of distant areas and of the entire skin. This is analogous to the assumed spread of hypersensitivity after application to the skin of substances producing sensitization of eczematous type (J. Jadassohn, H. Stauffer, and others).

It has been demonstrated, not only in cases of urticarial and eczematous hypersensitivity, but also in allergy to microorganisms, that the affected areas themselves and the skin in the vicinity of the affected areas are often more sensitive to the specific bacterial allergen than are distant areas tested at the same time. Using Warburg's method for determining anaerobic glycolysis, Boström and Hellerström[93] showed that the tissues of lesions of syphilis, tuberculosis, and *lymphopathia venerea* were much more sensitive to the respective specific allergen, than were clinically normal skin areas of the same patient. This new quantitative in vitro technic for demonstrating the degree of hypersensitivity of various tissues holds great promise as a much needed, accurate, objective, quantitative method.

In closing this year's review, I am glad to place in this final position of emphasis an article of general interest and particular value. Rackemann[94] repeats that which, I am sure, all allergists know, but which all of us occasionally forget. Rackemann reminds us that, not the theoretical considerations discussed above, nor the various technics and forms of skin testing—but accurate history taking and persistent detective work are the essentials for practical success.

And if this statement holds true for the allergist who deals primarily with asthmas and hay fevers, it holds doubly true for the dermatologist who is investigating cutaneous allergic diseases. For, in dermatologic allergy, the cutaneous pictures are kaleidoscopic and almost unbelievably variegated; and the number of the possible causal allergens is nearly infinite. Moreover, skin tests in dermatology often yield results which are valueless and even misleading, unless they can be viewed in the light of wide clinical experience, and unless they can be interpreted and found to be in conformity with the clinical characteristics, the history, and the future course of the dermatosis.

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Society Proceedings

THE ASSOCIATION FOR THE STUDY OF ALLERGY

KANSAS CITY, MO., MAY 9-12, 1936

Food Allergy as a Factor in Habitual Hyperthermia. L. P. GAY, M.D., St. Louis, Mo. (Abstract.)

Three cases were presented in which there had been a constant fever in each patient over long periods of time, and which had persisted after adequate treatment for presumed organic lesions. Although there was an unmistakable allergic history in each instance, the possibility of food allergy as a factor in producing fever had been ignored. The first patient had been treated for tuberculosis, although there were no physical signs to justify such a procedure. There was a history of hay fever and of food disagreements suggestive of a gastrointestinal allergy. The second patient had spent eight years in bed because of a persistent afternoon temperature elevation, but was told later that a positive diagnosis of tuberculosis, for which she had been treated, had never been established. As the fever and all other symptoms continued after eight years of bed rest and treatment, other explanations for the condition were considered advisable. An exhaustive physical examination was entirely negative, but there was a history of hypersensitive rhinitis, purpura, urticaria, joint pains, and a family history of allergy. The third patient had been having fever for two years, and after many presumably competent examinations had failed to show organic cause for her fever, she was told that there was no reason for her fever and to forget it. She had, however, a history of asthma in childhood, frequent and distressing attacks of urticaria, periodic headaches, a family history of asthma, and exhibited the physical signs of asthma at the time of examination. After a most complete search for organic disease in each case, attention was then turned to the possibility of allergy as a cause of fever. After a long and careful study, dietary restrictions were imposed and fever, as well as other allergic symptoms, disappeared in each individual. Experimental feeding of suspected allergenic foods was carried out repeatedly, and fever could be produced at will in this manner.

DISCUSSION

DR. SAMUEL H. WATSON, Tucson, Ariz.—Unfortunately, too many men, even those of us who think we know a little bit about allergy, seem to think that fever cannot be produced by allergy. I find in talking to doctors, a lot of them believe that if the patient has fever, that is an

argument against his having allergy, that fever means infection and excludes allergy. This is not true, as Dr. Gay has well shown.

An illustrative case came to Tucson from California, with a presumptive diagnosis of pulmonary tuberculosis. The only symptom present was cough, with a slight afternoon fever. On investigation, we found that the patient had formerly lived in the Middle West and gave a history of having had a cough for two years just prior to leaving there, which started in the late summer and disappeared with cold weather. In the light of what we found out later, this cough was probably caused by ragweed. This patient afterward moved to California where she lived for several years without any cough. Only a short time before coming to Tucson, she again developed a cough, particularly in the morning, and with this cough a slight afternoon temperature, 99.4° to 99.6.°

The doctor in charge had x-ray pictures taken, and the films showed an indecisive lesion. It might have been healed or not—one of those about which one just could not be sure. He found no other disease present to explain the symptoms and made a diagnosis of tuberculosis, by a process of elimination.

The patient decided if she was going to seek a cure for tuberculosis, she would like to go to the desert, so she came to Tucson. She was an intelligent woman, a teacher. She made a remark that it was odd, but that ever since she had been put to bed for tuberculosis her cough had been worse. That was when we began to go into this thing from an allergic standpoint, and we found her sensitive to feathers. We also found out that this woman had never slept on pillows until just about the time she began to have her symptoms, when a friend had given her a fine pair of down pillows. We took these away and the cough disappeared, and so did the fever. The girl was able to return to California and resume her work as a schoolteacher. Her presumed tuberculosis proved to be an allergy due to feather dust.

Dr. George Piness, Los Angeles.—Dr. Watson brings out a rather important observation, that foods and foods alone do not necessarily cause the symptoms that everybody has been discussing, but that any protein regardless of the source or its mode of entry, provided the patient is sensitive, might reproduce such a reaction.

If Dr. Gay will throw his slides on the screen it will be seen that he considers a drop of four to six hundred leucocytes as being a leucopenia, and, on the other hand, that he considers an increase of four to six hundred as a leucocytosis. In my opinion, these are neither evidences of true leucopenia nor leucocytosis. It seems to me, we should have a definite standard, and I think Dr. Vaughan has pointed out that there should be an increase or drop of at least a thousand or more to indicate leucopenia or leucocytosis. I do not think that anything particular was proved by the leucopenic indexes in the group presented today.

Dr. Watson's point is well taken, that one is too prone to believe that the presence of fever would exclude asthma. The fact is that most individuals do get fever reactions with protein shock.

Dr. Warren T. Vaughan, Richmond, Va.—Dr. Piness has quoted me correctly with regard to a drop of a thousand or more in the leucopenic index; on the other hand, we do sometimes see cases in which less than a thousand drop is of significance. We consider them as suggestive.

In my exhibit at the A. M. A. meeting, I have a very interesting chart of a patient who had a very slight drop (two or three hundred) to pork and had no symptoms. Two days later she ate pork again, and had migraine, and had a pronounced drop. In that case it was interesting to see that the leucocyte response corresponded to the presence or absence of clinical reaction.

That is one thing that makes the determination of an offending food so difficult; the fact that sometimes you can eat it with impunity and sometimes get into difficulty. In this particular case, when the patient ate it with impunity, there was no leucocyte drop.

Dr. French K. Hansel, St. Louis.—With the appearance of hyperthermia in cases of respiratory allergy, attention should be called to the importance of considering the possibility of the existence of acute infection. A mild acute infectious process in the nose accompanied by fever may be very difficult to differentiate from an allergic exacerbation on the basis of the clinical symptoms. By examination of the nasal secretions, however, one may determine which process is present. In allergy, a pure eosinophilia of the secretions is present, while in acute infection a pure neutrophilic response or an eosinophilo-neutrophilic response with a predominance of the latter is noted.

Dr. Albert H. Rowe, Oakland.—I have long been interested in the hyperthermia which results from food allergy, and I am glad to hear Dr. Watson's comment on the production of fever arising from inhalant allergy. I agree with Dr. Piness that inhalant allergy as a cause of many symptoms which are commonly due to food sensitization must be kept in mind, and is probably more common than we recognize today.

In my own experience, fever arising from food allergy has been encountered in children and in several adults, particularly in those suffering from gastrointestinal allergy and from toxemia associated with migraine. Such cause of fever has been reported occasionally in the literature. Hoag in 1924, recorded a case of severe, acne-like dermatosis in a boy who, because of temperature, was confined in a tuberculosis sanatorium. No evidence of tuberculosis was present, and later it was ascertained that milk allergy was responsible for the acne as well as the fever. He had never liked milk, but it had been forced on him during his sanatorium care. I have a similar patient who was in a sanatorium for one year because of an unexplained temperature. Milk, again, was the cause, not only of his gastrointestinal symptoms and severe acne, but also of his temperature. With an elimination diet, he rapidly became free of all of his symptoms including his fever.

Ample evidence in the literature exists, moreover, that fever frequently occurs during serum sickness and arises from various drug allergies, particularly from quinine and some of the coal tar products. In my monograph on food allergy, I have recorded experiences of various students, and of my own, with cases of unexplained fever due to food sensitization. So I think this paper is exceedingly important, not only for the members of our society but for the whole profession, and allergy must always be considered as one of the outstanding possibilities for unexplained fevers.

Dr. B. G. Efron, New Orleans.—I must call your attention to the fact that, in all of these cases presented today, I do not see adequate controls.

What happens, for instance, with reference to thrombocytopenia? Purpura occurs with and without thrombocytopenia. If you do enough platelet counts, you find that platelet counts are quite inconsistent, and often unreliable.

With reference to white cell counts: until such time as the normal diurnal variations have been ascertained, too much emphasis should not be placed on leucopenic responses following ingestion of foods. The assumption that by the ingestion of a certain food you are getting a specific allergic effect is unwarranted, since the foods and their extracts contain a large number of nonspecific substances.

Let me make myself a little clearer. It has been assumed that when you inject an allergic extract under the skin and get redness, swelling, and heat, your reaction is the result of the specific protein, whereas the reaction may very well be due to the nonspecific substances present in the allergen. You can induce fever by injecting milk, by injecting *B. coli,* and many other nonspecific substances.

Dr. Alan G. Cazort, Little Rock.—I believe Dr. Efron covered the point I wished to make in the fever cases. I have had some patients who apparently responded to food eliminations and additions, and one house-dust patient (due to mattress dust) who was kept in bed for several months with a tentative diagnosis of tuberculosis. But I wonder how many such cases have foci of infection, possibly of the sinuses, causing no symptoms ordinarily, but allowing absorption of toxic substances when drainage is prevented by allergic swelling; or possibly irritating foods may cause absorption of unusual substances from the gastrointestinal tract.

Of course the effect is the same, as far as the allergic factor is concerned, but I think there is a matter of scientific interest as to whether the fever is due to the allergen, or to other materials which allergens cause to be absorbed. The latter has been my impression.

Dr. Gay.—Dr. Piness has objected to the inclusion of foods that produce a preliminary leucopenia with a terminal leucocytosis in the list of incompatible foods. I am glad that Dr. Vaughan discussed this phase of the subject, as he explained the leucopenic index in a very satisfactory manner. I am sure, though, that Dr. Vaughan has seen in some of the cases on which he has done interval counts for several hours, that an initial leucopenia is sometimes followed by a hyperleucocytosis. I have started patients with a fasting count of five or six thousand, observed an initial leucopenia of a thousand or more, and after interval counts extending over a period of four or five hours, have found that the final leucocyte count was twenty thousand or above. This is the reason for a terminal leucocytosis rather than a leucopenia in some of the incompatible foods, but a reaction of this type, according to my observation, is indicative of a toxic allergen and its recognition is of extreme importance.

Prolonged fever, such as is associated with actual tuberculosis, or that seen in an acute infection, is just as likely to relieve allergic symptoms temporarily as is an injury or an operation. Relief of symptoms in an individual with a gastrointestinal allergy is quite common after an operation, and it is not unusual that the removal of a perfectly normal appendix will give that individual relief from symptoms for months.

This is not permanent as the gastrointestinal symptoms will return, and I feel that the same association is true of fever due to an infection.

The answer to Dr. Efron is as follows: "I make no effort to determine what protein fraction is causing the reaction and furthermore I do not care. I do not care because the patient comes for relief of distressing symptoms, and if, by taking such foods as string beans, potatoes, or pork out of his diet, without fretting about what particular protein fraction is the cause of the trouble, we make that individual a perfectly healthy, self-supporting, and happy citizen again, I think that we have accomplished our purpose."

Selected Abstracts

Asthma and Hay Fever

UNDER THE DIRECTION OF SAMUEL FEINBERG, M.D., CHICAGO

Further Studies of the Pollen Content of the Melbourne Air. Sharwood, M. M.: M. J. Australia **1**: 4, 1937.

The author has continued his pollen study of Melbourne, Australia. The grass season, which accounts for most of the pollen and hay fever symptoms, begins the latter part of September, reaches a peak about the middle of November, and is practically over by January, although a small amount of the pollen prevails until March. The plantain, beginning at about the same time as the grasses, has its maximum flowering period in December and continues with fair amounts until March. Sorrel and dock vary with the amount of plantain. *Chenopodium* pollen is very small in amount. The tree season is from about August to October, and although the pollen production is considerable, the author is not aware of any sensitization to these pollens. The elm produces the greatest amount of pollen, while the pine also produces a fair quantity. The oak, beginning to pollinate the first part of September and continuing until the first part of October, apparently yields very little pollen. The author observes an inverse relationship between the pollen count and the relative humidity.

Hypersensitivity to Acetylsalicylic Acid (Aspirin). Prickman, Louis E., and Buchstein, Harold F.: J. A. M. A. **108**: 445, 1937.

Of 62 cases of hypersensitivity to aspirin, all but one gave a history of either personal or familial allergy. All of the commonly accepted major allergic syndromes except eczema, were encountered as manifestations of hypersensitivity, with the respiratory mucous membrane by far the most commonly reacting tissue, and gastrointestinal tract next. The reaction is usually an exacerbation of the patient's allergic disease. Speed of reaction varies from ten minutes to two hours after ingestion. Reactions occurring later than three hours after ingestion of acetylsalicylic acid, are probably not due to true allergic sensitivity.

Asthma is the most serious form of reaction, all fatal cases having been of this type. Epinephrine and morphine are relatively ineffective in severe cases. Skin tests are nearly always negative. For diagnosis, Duke suggests placing a small speck of acetylsalicylic acid in the mouth. In allergic individuals, symptoms will appear in one minute. Passive transfers were negative. Patients with nasal polyps suffered the most severe reactions.

Treatment consists of avoidance of preparations containing acetylsalicylic acid and the use of adrenalin, morphine, and oxygen. If acetylsalicylic acid remains in the mouth, Duke advises rinsing the mouth repeatedly with a teaspoonful of vinegar, or dilute acetic acid to a glass of water.

Problems in the Treatment of Hay Fever. Withers, O. R.: J. Kansas M. Soc. **37**: 444, 1936.

Withers emphasizes the importance of a consideration of the variable factors in hay fever. Extra-pollen sensitiveness, such as food, epidermal, or mold allergy,

is often a stumbling block to treatment unless recognized. The degree of sensitivity of the individual must be taken into account, and is not always to be judged on the basis of the intensity of the skin reaction. The pollen content of the air is a variable, affecting practically all hay fever patients, and is to be considered both in the interpretation of the results of the treatment and in the intensity of treatment. Desensitization and the type of response to it is an individual variable. The author believes that adrenalin should not be employed to minimize the reaction. He believes that because of the slight local reaction thus produced, it may interfere with the production of an immune response.

Atmospheric Causes of Allergy in Western Washington. Schonwald, P.: Northwest Med. **36**: 14, 1937.

Schonwald made an air study of Seattle and correlated it with hay fever and asthma symptoms. A number of trees are important, among which are hazel, alder, birch, poplar, balm of Gilead, cedar pine, oak, maple, mountain ash, cedar, tamarack, and red fir. The tree season is from February until July. The grass season, due to June grass, orchard grass, rye and velvet grass, occurs from April until August. The plantain season is important and extends from May until frost. In addition, lamb's-quarters, curly dock, sheep sorrel, and pigweed are hay fever weeds.

The author has found also the spores of brake fern to cause symptoms in some patients. He has found, too, that mold spores are frequently a contributing cause, and in many instances even the sole cause of allergy. The most common fungi found by him in the Seattle area are *Rhizopus, Aspergillus, Penicillium, Hormodendrum* and *Trichoderma.*

Asthma and Allergic Rhinitis From Molds. Feinberg, S. M.: Lancet **57**: 87, 1937.

A series of 90 cases of mold hypersensitiveness are analyzed by the author. There is shown a decided tendency to seasonal aggravation among the mold sensitive patients in the Chicago area. Of the 90 patients, 70 began their first symptoms before the age of ten. Nasal symptoms alone were present in 26, asthma alone in 9, while 55 had both nasal and asthmatic symptoms. Mold allergy alone was present in 25, while 58 had definite associated pollen allergy. Of the total group, 60 had specific treatment with mold extracts, which resulted in excellent results in 48, fair in 9, and failure in 3. The conclusion is made that mold allergy is not a rarity but a common entity.

The Control of Allergic Manifestations by Phenylpropanolamine (Propadrin) Hydrochloride. Black, J. H.: Lancet **57**: 101, 1937.

Black found that propadrin hydrochloride, which is an analogue of ephedrine, is capable of giving relief in hay fever, asthma, and urticaria, similar to that given by ephedrine. It was preferable to ephedrine in many instances because it did not produce symptoms of nervousness or insomnia. The doses used were 24 to 48 mg.

Sensitization to Milk as a Result of Its Use in Nonspecific Foreign Protein Therapy. Bernstein, C., Jr., and Ginsberg, J. E.: J. A. M. A. **108**: 193, 1937.

A woman who had severe chronic asthma, and who failed to respond to any form of treatment, was finally given nonspecific treatment in the form of defatted milk hypodermically. The beginning dose was 0.02 c.c., which was increased to about 0.8 c.c. The therapeutic response was satisfactory. At about the sixteenth dose,

local reactions began to be noted and on the twenty-fourth dose (0.4 c.c.) prompt shock with asthma resulted. The authors warn against the use of nonspecific protein therapy in allergic individuals, particularly when it involves the use of material closely related to proteins to which they are apt to be exposed.

Delayed and Immediate Reactions to Bacterial Nucleoproteins in Asthma, Hay Fever, and in a Group of Miscellaneous Diseases. Stevens, F. A., and Jordani, L.: J. Immunol. **31**: 477, 1936.

Pursuing further their work on the skin reactions to bacterial nucleoproteins, the authors have found that reactions of the immediate type are confined almost exclusively to those having asthma or hay fever, or other atopic manifestations. They do not believe that it is the trace of polysaccharide attached to the protein which is responsible for this reaction.

The Treatment of Allergic Conditions With Amino-Acetic Acid. Beard, H. H., and Thiberge, N. T.: Medical Record **145**: 254, 1937.

The results obtained in asthma with the hydrolytic products of proteins led the authors to the use of amino-acetic acid (glycine). The latter was given orally in daily doses of 10 to 20 gm. dissolved in water or fruit juices. In a series of 10 patients, with asthma or other allergy, improvement was noted in the majority.

Dermatology

UNDER THE DIRECTION OF MARION B. SULZBERGER, M.D., AND JOSEPH GOODMAN, M.D., NEW YORK CITY

Fatal Iododerma. Hollander, Lester, and Fetterman, George H.: Arch. Dermat. & Syph. **34**: 228, 1936.

Hollander and Fetterman present a case of fatal iododerma. In the 10 cases previously reported in the literature, there was a definite history of ingestion of iodine. Here, too, a history of ingestion of iodine (yellow mercurous iodide) was obtained. The patient, male, aged sixty-five years, was given intravenous injections of sodium chloride, and the skin lesions were treated with superficial x-ray and moist dressings. The patient died of bronchopneumonia nine months after he was first seen.

Chemical examination of a lesion excised one month before the patient's death showed 470 mg. iodine per Kg. tissue. The autopsy report is given in detail.

The authors mention that the German writers attribute these serious or fatal forms of iododerma to a sensitivity to iodine.

Desensitizing Effect of L-Ascorbic Acid (Vitamin C). Dainow, I. (Geneva): Ann. de dermat. et syph. **6**: 830, 1935.

Dainow has noted that l-ascorbic acid administration is of great desensitizing value in allergic conditions.

Five cases have been observed: (1) a patient with arsphenamine (erythematopapular) dermatitis was relieved of his skin affection and made tolerant to arsphenamine by administration of ascorbic acid (3 daily intravenous injections of 0.05 gm. in 10 c.c. water); (2) a patient with severe exfoliative arsphenamine dermatitis

was given ascorbic acid orally (3 tablets of 0.05 gm. daily). Improvement was rapid. The 3 other cases were similar to (2).

The author believes that ascorbic acid will profoundly modify the clinical evolution of arsphenamine dermatitis and completely change its prognosis.

Treatment of Herpes With Ascorbic Acid. Dainow, I.: Ann. de dermat. et syph. **7**: 817-827, 1936.

Dainow reports favorable results in treating herpes and herpes zoster with vitamin C (ascorbic acid). Administration of vitamin C in herpes zoster affects not only the erythema and vesicles, but also soothes the pain usually accompanying these conditions. He concludes that this action of vitamin C in cases of herpes and herpes zoster is explained by the very nature of these infections; their pathogenic agent is supposed to be filtrable and located in the nerve centers. And it has been shown (Melka Plaut and v. Bulow) that considerable amounts of vitamin C are present in the nerve centers; and that these quantities of vitamin C can be influenced by administration of ascorbic acid. Thus, it can be deduced that vitamin C has its effects directly on the herpes virus and on the pathogenic agent of herpes zoster.

Allergy in Chronic Trichophytosis of Adults. Maschkilleison (Medical Inst., Woron): Arch. f. Dermat. u. Syph. **174**: 413, 1936.

Maschkilleison believes that chronic dermatophytosis of the glabrous skin has an exogenous origin in adults, and states that adults thus affected react little or not at all to trichophytin. Specific serum examinations as well as complement fixation tests with the fungus antigen also give negative results.

The author reports the following studies: (1) A man with normal skin and negative trichophytin reaction was inoculated (Bloch) with a Trichophyton *gypsum* culture, obtained from a patient with chronic dermatophytosis of the glabrous skin. An acute trichophytid resulted. (2) A woman with chronic superficial dermatophytosis was inoculated with a culture of Trichophyton *gypsum* from a trichophytosis *capitis* lesion of a child. An autogenous culture of Trichophyton *violaceum* was simultaneously injected, and elicited no reaction; whereas the site of the *gypsum* injection reacted typically. The previously weak trichophytin reaction was now strongly positive. The same experiment repeated in four other patients gave the same results. (3) A girl, aged nineteen, with a chronic trichophyton infection and a mild trichophytin reaction received an injection of Trichophyton *gypsum* culture from another patient with superficial dermatophytosis, together with autoinoculation. The result was the same as above.

The author concludes that the skin of adults with chronic superficial trichophytosis evidently reacts hyperallergically to the alien fungus, while it exhibits hypoallergy to its own parasite.

Fifteen Cases of Eczema Due to Dyed Clothing. Bonnevie, Poul, and Genner, Viggo (Copenhagen): Acta dermat.-venereol. **17**: 457-465, 1936.

The authors report 15 cases of eczema due to dye in clothing. The patients were chiefly women. The axillae, flexural surfaces of the elbows, and the lateral and posterior surfaces of the neck were the areas of predilection; contributory factors were found in hyperhydrosis, and the use of depilatories in the axilla. Obesity, heat, and pityriasis simplex of the scalp were other predisposing factors. The one male case developed eczema following the wearing of a new blue suit. In all cases it was found that the fabrics of the offending clothing were of cheap quality; and that blue clothing was always the offender.

Using Jadassohn's epicutaneous test (patch test), 10 cases were shown to be positive for blue dye, and 2 were negative. In 3 cases this test was not performed. Besides being hypersensitive to the dye of their clothing, some of the patients also gave positive reactions to the dyes in pure form.

The authors suggest that the sensitization of some of these patients may have been brought about through a previous application of some dye to the eyebrows or hair. Several of the patients also gave positive patch tests with substances of a different nature, e.g., Persil (a soap powder), bichloride of mercury, pinen, coal tar, wood tar, and primulin.

Immunology

UNDER THE DIRECTION OF MATTHEW WALZER, M.D., BROOKLYN

Relation Between Antianaphylaxis and Antibody Balance. I. The Rôle of Excess Circulating Antibody in Hypersensitiveness. Morris, M. C.: J. Exper. Med. **64**: 641, 1936.

The author presents experimental evidence against the theory that anaphylactic shock is determined by the reaction of the injected antigen with antibody that is already fixed, and that a high concentration of circulating antibody offers protection against this cellular action and subsequent shock.

Guinea pigs, passively sensitized by intraperitoneal injections of rabbit antisera, were used for the experiments. The antigens used for producing the antisera in rabbits were crystalline egg albumen, horse serum, and a bacterial polysaccharide.

The author shows that passively sensitized guinea pigs receiving normal rabbit or guinea pig serum, prior to the injection of antigen, may be protected against the injection of lethal doses of antigen. In this respect, foreign serum affords a greater protection than does homologous serum. Sensitized guinea pigs injected with specific antiserum, prior to receiving the antigen intravenously, show no greater refractoriness to anaphylaxis than do those injected with serum lacking the specific antibodies. Instances are recorded where the injection of an excess of antibodies into the circulation led to an increased degree of sensitivity.

Hence, it is suggested that the degree of anaphylactive sensitivity is determined by both the circulating and fixed antibodies, and that excessive circulating antibody increases rather than decreases the degree of sensitivity of the animal.

Studies in Experimental Hypersensitiveness in the Rhesus Monkey. II. Passive Local Cutaneous Sensitization With Human Reaginic Sera. Straus, Henry W.: J. Immunol. **32**: 251, 1937.

The author describes the successful passive local sensitization of the skin in 16 of 17 Rhesus monkeys, using various human reagin-bearing sera.

These were usually used in undiluted form and about 0.05 c.c. to 0.1 c.c. was injected intracutaneously. The interval between sensitization and testing varied from twenty-four hours to six days. Most of the tests were done after an interval of forty-eight hours. Testing of the passively sensitized sites was performed by the intracutaneous or intravenous injection of the specifically related atopen. After an interval of one and one-half to five minutes, a wheal formed, measuring as much as 5 cm. in diameter. It reached its maximal proportions within thirty minutes and then faded slowly, being discernible, however, in some animals six hours after the onset of the edema. Erythema was noted on only one occasion. Pruritus seemed to be absent.

Sixteen of 17 monkeys accepted sensitization with various human sera containing reagins for horse serum, peanut, cottonseed, and flounder. The titer of the sensitizing serum was found by the author to be an important factor in sensitization. The specific nature of the cutaneous sensitization was conclusively demonstrated.

Anaphylactic Sensitization With Chemically Definite Compounds. Fiers, H. E., Jadassohn, W., and Stoll, W.: J. Exper. Med. **65**: 339, 1937.

Jadassohn and Schaaf were able to sensitize guinea pigs by means of diazotized atoxyl coupled with guinea pig serum. This is in agreement with Wolff-Eisner's hypothesis that drugs couple with protein molecules in the body to produce sensitization. The present communication is offered as further proof of this hypothesis. Guinea pigs were injected intraperitoneally at weekly intervals with a 1 per cent solution of sodium atoxyl-diazoamino-sulfoanthranilate and tested for sensitivity from fifty-two to eighty-eight days after the fourth injection by the Schultz-Dale technic. Of five animals tested in this manner with the sensitizing solutions, none showed positive reactions. Of 10 animals tested with diazotized atoxyl coupled with chicken serum, all showed evidences of specific hypersensitiveness. Previous tests with sodium atoxyl-diazoamino-sulfoanthranilate did not inhibit or prevent the reactions with the azoprotein. These results suggest that the injected sodium atoxyl-diazoamino-sulfoanthranilate decomposes in vivo and couples with body protein to form a corresponding azoprotein which sensitizes.

The Relation Between Antianaphylaxis and Antibody Balance. II. The Effect of Specific Desensitization Upon Resistance to Infection and Upon Antibody Balance. Morris, M. C.: J. Exper. Med. **64**: 657, 1936.

The author presents further evidence to prove that antianaphylaxis is not caused by a partial saturation of cellular or humoral antibodies. Experiments are presented to show that guinea pigs which are passively sensitized with antihorse serum, and then specifically desensitized, cannot be as easily resensitized with the same serum as before. Animals which are sensitized with antipneumococcus serum and are specifically desensitized, do not accept subsequent passive sensitization with antihorse serum to a normal degree. The desensitization with specific carbohydrate in animals sensitized with anti-Friedlander Type B serum, does not reduce the resistance of these guinea pigs to infection with this organism. The author also shows by mouse protection tests with the sera of sensitized and desensitized guinea pigs, that desensitization cannot be readily accounted for on the basis of diminution of circulating antibodies. The author, therefore, concludes that antianaphylaxis is a state of refractoriness which cannot be accounted for either by an excess or depletion of circulating antibody, but is due to some secondary unknown factor.

Serum Disease and the Therapeutic Effect of Diphtheria Antitoxin. Davidsohn, I., and Hunt, L. W.: Am. J. Dis. Child. **52**: 1324, 1936.

The authors studied the therapeutic effect of horse serum antitoxin, administered to a group of 40 patients with diphtheria, who reacted to the injection with immediate or accelerated serum reactions within a period of forty-eight hours. They compared the results obtained in this group with those in another series of 164 patients, who experienced the usual type of serum disease, and a third group of 97 patients, who manifested no serum symptoms of any type.

The average severity of the illness in all three groups before the administration of the antitoxin was apparently the same. No difference could be noted in the

therapeutic effect of the antitoxin in the patients with ordinary serum disease, as compared to those without any serum reactions. Results were less satisfactory, however, in patients who experienced immediate serum reactions. The incidence of complications in this group was also higher than in the others. The authors therefore advised that whenever the administration of a horse-immune serum for passive immunization is followed by an immediate or markedly accelerated serum reaction, the patient be given additional doses of serum, preferably in the form of an antitoxin prepared from an animal other than the horse.

Otolaryngology

UNDER THE DIRECTION OF FRENCH K. HANSEL, M.D., ST. LOUIS

A Statistical Study of Allergic (Vasomotor) Rhinitis. Clarke, J. A., Jr., and Rogers, Harry L.: Arch. Otolaryng. **25**: 124, 1937.

Clarke and Rogers report a statistical study of 162 cases of allergic or vasomotor rhinitis. It is noteworthy that 73 per cent of the patients had already had one operation, and 20 per cent had two or more operations on the nose and throat. Fifty-one per cent showed positive skin reactions to one or more inhalants, although in only 10 per cent were the reactions markedly positive. All tests were done by the intracutaneous method. This series of patients did not include those patients reacting to pollen. House dust was found to be the most frequent cause of reactions producing positive reactions in 75 or 46 per cent of the entire series. Next in frequency were feathers and orris root. There were only seven reactions to food.

Contribution to the Treatment of Vasomotor Rhinitis. Lewy, Alfred: Laryngoscope **47**: 100, 1937.

In addition to ionization, the use of escharotics locally has been employed by recent observers in the treatment of nasal allergy. Lewy recommends the local use of resorcinol. He states that the proportion of successes has been considerably greater than with any other treatment, and the reaction less. Resorcinol is applied in the form of a watery paste over the entire nasal mucosa including the middle meatus, after a preliminary application of 3 per cent cocaine. He found that relief from this treatment may last for a few weeks to several months, and in a number of cases treated about two years ago there have so far been no recurrences. Its use in the treatment of ragweed hay fever has not been encouraging.

Asthma and the Nose. Jacquelin, A., and Chait, A.: J. Laryng. & Otol. **52**: 197, 1937.

A study of the frequency of nasal lesions in asthma and the value of operations on the nose in such cases was reported by Jacquelin and Chait. Four hundred and thirty patients were studied. In 48 cases the nose was found to be obstructed, and in 26, infectious manifestations, such as rhinitis and sinusitis, were noted. Various operative procedures, such as irrigations of the sinuses, resection of the septum, etc., were undertaken. On the whole, while the condition of a small number of patients improved, many showed no amelioration, and several even became worse. It was concluded that asthma in itself is no indication for nasal operations.

Is Ionization Worth While for the Allergic Patient? Alden, Arthur M.: Laryngoscope **47**: 17, 1937.

A recent report by Alden on ionization of the nasal mucosa in allergy summarizes his observations to date. He states that certainly desensitization is still the method

of choice in the treatment of nasal allergy, with ionization being reserved for those cases where the obstructive and secondary symptoms are predominant, and where the mechanical relief to be expected is more than commensurate with the tissue damage incident to ionization. He found that asthma was not lessened after ionization, except in a few cases. He finally concludes by stating that ionization produces in the nasal mucosa a mechanical change which renders it less susceptible to vascular and secretory reactions. He does not believe that ionization alters either the allergic status of the individual, or the ability of the nasal cells to be affected by allergens. Finally, he points out that the value of ionization rests solely upon its efficiency as an agent to reduce excessive nasal intumescence, and hypersecretion.

Pediatrics

UNDER THE DIRECTION OF WILLIAM C. DEAMER, M.D., SAN FRANCISCO

The Allergic Diseases in Childhood. Urbach, E.: Arch. f. Kinderh. **109**: 91, 1936.

This is a brief summary of Urbach's views on classification and methods of study and treatment. He employs the terms allergy, parallergy or metallergy, and pathergy. Allergy refers to the reaction caused by specific antigen-antibody mechanism, parallergy and metallergy, to reactions caused by nonspecific antigens in a specifically sensitized individual (parallergy where this reaction differs from that of the specific antibody, and metallergy where it is the same type of reaction). Pathergy refers to all hyper- and hypo-sensitive processes, which according to present views, do not involve an antigen-antibody reaction. He employs the patch test in eczema, cutaneous or intracutaneous tests in neurodermite, direct mucous membrane applications in mucous membrane allergy (pollen, flour, oil, etc.) and occasionally inhalation tests in bronchial allergy. He finds the skin tests almost always negative in food allergy, and employs trial diets with or without propeptan tablets prepared for specific foods. In treatment he mentions desensitizing by applications, sprays or injections, deallergizing with specific propeptans, metaspecific desensitization with intramuscular peptone injections or tuberculin and antipathergic therapy with drugs, x-ray or psychotherapy.

Urbach finds that hay fever has increased remarkably in recent years and almost entirely in the intelligent middle or upper classes of the city. He treats seasonally by four daily oral doses of a preparation of the seed, not the pollen, of the grass, weed or tree concerned. Acid and pepsin are given simultaneously. Results are very satisfactory.

The Allergic Basis of Primary Purpura in Children. Bartley, C. H.: Lancet **2**: 359, 1936.

In a follow-up study of 12 cases of primary purpura, in children, including purpura simplex, Henoch's purpura, and Schönlein's purpura, the author concludes that it is fallacious to label primary purpuras as allergic, since the patients often show none of the attributes of allergy and the course of the disease makes an allergic basis seem improbable. Only two of the 12 patients had a clear-cut family or personal history of allergy. In five, there were signs of septic infection preceding the purpura. None had a recurrence during an interval of one to nine years. He warns against "forcing the anaphylactoid key into locks which it was never destined to fit, which practice today threatens to impair its usefulness." No blood studies, skin tests, or elimination procedures are mentioned.

Concerning the Sudden Death of an Infant With Eczema. Woringer, P., and Oudet, P.: Rev. franç. de pédiat. **12**: 660, 1936.

A fifteen-month-old infant had had eczema since three months of age. She was undernourished and had contracted measles, varicella, and otitis media during her first year. She was brought to the hospital eight days after she had contracted cutaneous diphtheria on the scalp and face, superimposed on the eczema. There was considerable local and periglandular edema. She was given 20 c.c. of antidiphtheritic serum. The child's condition did not change until the next day when it showed progressive signs of myocardial failure, and she died within a few hours. An autopsy was not done. Diphtheritic intoxication was thought to have played a part in the fatal outcome.

Attention is called to the fact that in several sudden eczema deaths, autopsy reports have been negative, some have suggested a thymicolymphatic state, and to others the "Herztod" deaths described by German authors, in some of which myocardial degeneration and lymphocytic infiltration have been found.

Thrombopenic Purpura Induced by Pertussis Toxin in Allergic Children. Kugelmass, I. N.: J. A. M. A. **107**: 2120, 1936.

Three allergic children developed thrombocytopenic purpura following subcutaneous injection of *B. pertussis* vaccine obtained from different sources. Presumably the usual procedure of three injections, each a week apart, was followed. The purpura appeared ten days, two weeks, and three weeks after the last immunizing injection. In one case, purpura recurred two and three months later. In another case, purpura had occurred ten months prior to the first injection of vaccine. In one child, death resulted from cerebral hemorrhage when the purpura was later aggravated by the development of a paroxysmal cough.

Allergic Abdominal Pain in Children. Fries, J. H., and Merrill, G. A.: Am. J. Dis. Child. **52**: 1107, 1936.

A general discussion and four case reports are given. In diagnosing allergic abdominal pain eosinophile counts and skin tests were not considered particularly helpful. A less than average normal response of acid secretion to an alcohol test meal was found in a majority of the patients studied. Hypertonicity and hyperperistalsis of the intestines as shown by roentgenogram were found to be characteristic, and in addition pyloric spasm and delayed emptying of the stomach were seen. Dilute hydrochloric acid by mouth was found to be the most useful therapy. The authors warn against mistaking the condition for an acute surgical abdomen. They do not mention the number of patients studied.

Bronchiectasis as a Complicating Cause of Asthma. Chobot, R.: Am. J. Dis. Child. **52**: 882, 1936.

An eight-year-old boy complained of asthma of four years' duration. He had had pertussis, measles, and eczema, and there was a family history of allergy. Early emphysema but no clubbing was present. The roentgenogram of the chest was considered typical of bronchial asthma. Tests were negative and diet trials and vaccine therapy were without benefit. The patient became steadily worse. After fourteen months' study, in spite of a second negative roentgenogram of the chest, bronchoscopy was performed and bilateral bronchiectasis with two fair-sized cavities was demonstrated. Aspiration of the cavities every three weeks brought about marked improvement.

Nutrition of Children on a Vegetable Diet. III. Growth and Allergy. Lane, B. S.: Am. J. Dis. Child. **52**: 1397, 1936.

A group of children, including seven-year-old twins, were raised on an exclusively vegetable diet, including one and a half to two pints of almond-lac daily. They grew and developed exceptionally well, and so far as could be determined none developed allergic symptoms with the prolonged use of this combination of almond, peanut, soybean, and vegetables. Its use was also successful in many cases of infantile eczema. In certain instances, the author attributed the eczema to an altered metabolism due to dietary errors which almond-lac corrected, rather than to hypersensitiveness.

Concerning the Biological Value of Certain Eczema Diets. Brock, J.: Monatschr. f. Kinderh. **68**: 365, 1937.

Brock find that the diets employed in infantile eczema are frequently low in fat, usually deficient in sodium chloride, and practically always contain a vegetable protein to replace the animal protein of milk. To test whether vegetable protein alone sufficed, he used 15 different diets in white rats. Gliadine from wheat gave a poorer weight gain than either gliadine plus a small amount of liver or two vegetable proteins: gliadine plus banana. Similarly almond milk "Nuxo" gave a poor weight gain. On the other hand, foods deriving their protein from bran "Materna" and soybean "Lactopriv" gave good weight gains. The addition of salt to the salt-poor preparations did not bring any demonstrable improvement in rate of gain either clinically or in rats.

Miscellaneous

The Treatment of Allergic Disorders With Magnophyllin and Histamine. Dzsinich, A., and Paul, B.: Klin. Wchnschr. **15**: 1754, 1936.

In allergic diseases, the lesion is an edema wherein water enters the tissues and is bound there. In some instances this is reflected by high hematocrit readings. Theocin compounds have the property of mobilizing water in the blood stream, and of those, Magnophyllin is very effective. It is, therefore, indicated in allergic disturbances. Histamine is likewise indicated as it appears to have the property to desensitize tissues so that they lose the capacity to form allergic lesions.

A combination of the two drugs has been devised. Magnophyllin is given in 10 c.c. doses (sec. Richter) intravenously every day. Histamine is given separately, and is injected subcutaneously also daily. The initial dose is 0.00001 mg., which is increased gradually to 0.01 mg.

This combination of drugs was used in asthma, urticaria, vasomotor rhinitis, and vernal conjunctivitis, and the reported results are encouraging.

Ion Concentration of Allergic-Hyperergic Inflammation. Kuepper, R.: Klin. Wchnschr. **18**: 188, 1937.

Acting upon the observation of Schade, that inflammation is usually accompanied by an acidosis of the tissues as measured by an increase of hydrogen ions, the author tested allergic-hyperergic infiltrates to detect a possible difference. He found the pH of such infiltrates presented alkaline values. This observation suggests that effect calcium therapy in allergy is probably excited by way of this acidosis, rather than by merely reducing capillary permeability. Likewise in rheumatic fever, which is considered an allergic inflammation, the benefit of salicylic acid may act by inducing tissue acidosis to counteract tissue alkalosis of allergy.